

**THE EUROPEAN AGENCY
FOR THE EVALUATION OF
MEDICINAL PRODUCTS**



**FOURTH
GENERAL
REPORT**

1998



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**FOURTH GENERAL REPORT
ON THE ACTIVITIES OF THE EUROPEAN
AGENCY FOR THE EVALUATION OF
MEDICINAL PRODUCTS**

1998

Adopted by the Management Board on 2 December 1998

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EMA mission statement

To contribute to the protection and promotion of public and animal health by:

Mobilising scientific resources from throughout the European Union to provide high quality evaluation of medicinal products, to advise on research and development programmes and to provide useful and clear information to users and health professionals

Developing efficient and transparent procedures to allow timely access by users to innovative medicines through a single European marketing authorisation

Controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues in food-producing animals

This annual report is presented to the Management Board by the Executive Director in accordance with Article 55(3) of Council Regulation (EEC) No 2309/93. It is forwarded to the European Parliament, Council, Commission and Member States. It is available on request in all official EU languages.

Previous annual reports and other reference documents are available from the Office for Official Publications of the European Communities. Further details are set out in Annex 8.

This report covers activities of the EMA in 1998. Chapter 1 sets out the activities of the Management Board, the Agency's partnership with national competent authorities and other general aspects of the EMA, including transparency and international activities.

The operational and technical work of the EMA in 1998 is reported in Chapter 2 on human medicines, Chapter 3 on veterinary medicines and Chapter 4 on technical coordination, including the work of the European Technical Office for Medicinal Products (ETOMP) and the European Pharmacopoeia. Administration and accounting matters are described in Chapter 5.

The Report, in accordance with Article 15c(1) of Council Directive 75/319/EEC, as amended, and Article 23c(1) of Council Directive 81/851/EEC, as amended, also summarises the operation of the decentralised procedure during 1998.

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Overview of the European authorisation system

Human and animal health

The European system for the authorisation of medicinal products for human and veterinary use has been in place since 1995. It is designed to promote both public health and the free circulation of pharmaceuticals. Access to the European market is facilitated for new and better medicines – benefiting users and European pharmaceutical research.

In the case of veterinary medicinal products, consumer and animal health is protected through the fixing of maximum residue limits in food-producing animals.

EMA – a network agency

The new European system is based on cooperation between the national competent authorities of the Member States and the EMA. The EMA acts as the focal point of the new system, coordinating the scientific resources made available by Member State national authorities, including a network of some 2 200 European experts.

The EMA is designed to coordinate the existing scientific resources of the Member States, acting as an interface between the national competent authorities rather than as a highly centralised organisation. The partnership between the EMA, national authorities and the European Union institutions is central to the successful functioning of the European authorisation procedure.

The European procedures

The new European system offers two routes for authorisation of medicinal products:

- *Centralised procedure:* Applications are made directly to the EMA, leading to the granting of a European marketing authorisation. Use of this procedure is compulsory for products derived from biotechnology, and optional for other innovative medicinal products.
- *Decentralised procedure:* Applicable to the majority of conventional medicinal products. Applications are made to the Member States selected by the applicant and the procedure operates by mutual recognition of national marketing authorisations. Where this is not possible, the EMA is called on to arbitrate.

Opinions adopted by the EMA scientific committees in either the centralised procedure or following arbitrations lead to binding decisions adopted by the European Commission.

Purely national authorisations remain available for medicinal products to be marketed in one Member State.

Foreword

by Strachan Heppell
Chairman of the Management Board



1998, like 1995, marked an important step in the evolution of the European system for the evaluation of medicines. Since the beginning of 1998, it has no longer been possible for a new medicine to be given market authorisation under a national system of approval unless it is to be marketed only in that country. This further development did not disrupt the European system. It was very much business as usual, with performance continuing to improve. This report makes that clear.

The fact that the new system has coped well with change is a tribute to the hard work and management skills of all those concerned in the EMEA and in the national authorities, the national experts, the regulatory staff in the pharmaceutical companies and in the European Institutions, especially the European Commission.

It has also demonstrated the value of incremental change. The European system has been built up step by step. Recognising this, the Management Board has spent much of its time during the year on the challenges ahead, alongside its oversight of current business.

The Board considered two issues in particular. The first was the forthcoming review of the system by the European Commission, as is required by Regulation (EEC) No 2309/93. The second was a project to provide better and more accessible information about the efficacy of medicines, called the Medicines Information Network for Europe (MINE).

The Management Board expects the review to examine how well the system has worked and as part of that how well the EMEA has performed. It is also reasonable to assume that the review will consider the changing environment in which the new system will operate. The Board will stand ready to offer whatever help it can in the review.

The aim of the MINE project will be to collect and validate information about the efficacy of medicines and then make it easily accessible to health care professionals and the public. The first stage will be a pilot project to collate and make available electronically summaries of product characteristics and patient leaflets. The results of the pilot project, which will be carried out with the help of the European Commission, will be carefully evaluated before further proposals are made.

The MINE project will be a cooperative venture, where the Agency's role will be to harness the knowledge and judgment of professional networks across Europe, including universities and public agencies. The EMEA will work closely with national authorities, who I anticipate will take responsibility for relating the data to national circumstances and making it available at the national level. I also hope that the project will involve other key interests, including health care professionals and management, patient and consumer bodies and the industry bodies concerned.

Introduction

By Fernand Sauer
Executive Director



The EMEA has now completed its fourth year of successful activity. Our continuing commitment to transparency, closer partnership with experts from the national authorities and implementation of quality management have all played together to create a solid reputation as a professional and scientifically independent organisation.

Greater transparency is an important element in ensuring that the EMEA is accountable to its institutional partners; the European Parliament, Commission and Member States. Efforts in 1998 for even greater transparency for users, health professionals, industry and the general public has inevitably lead to closer scrutiny. Through its continuing dialogue with all interested parties the EMEA is working to address concerns raised and ensure a more rigorous system.

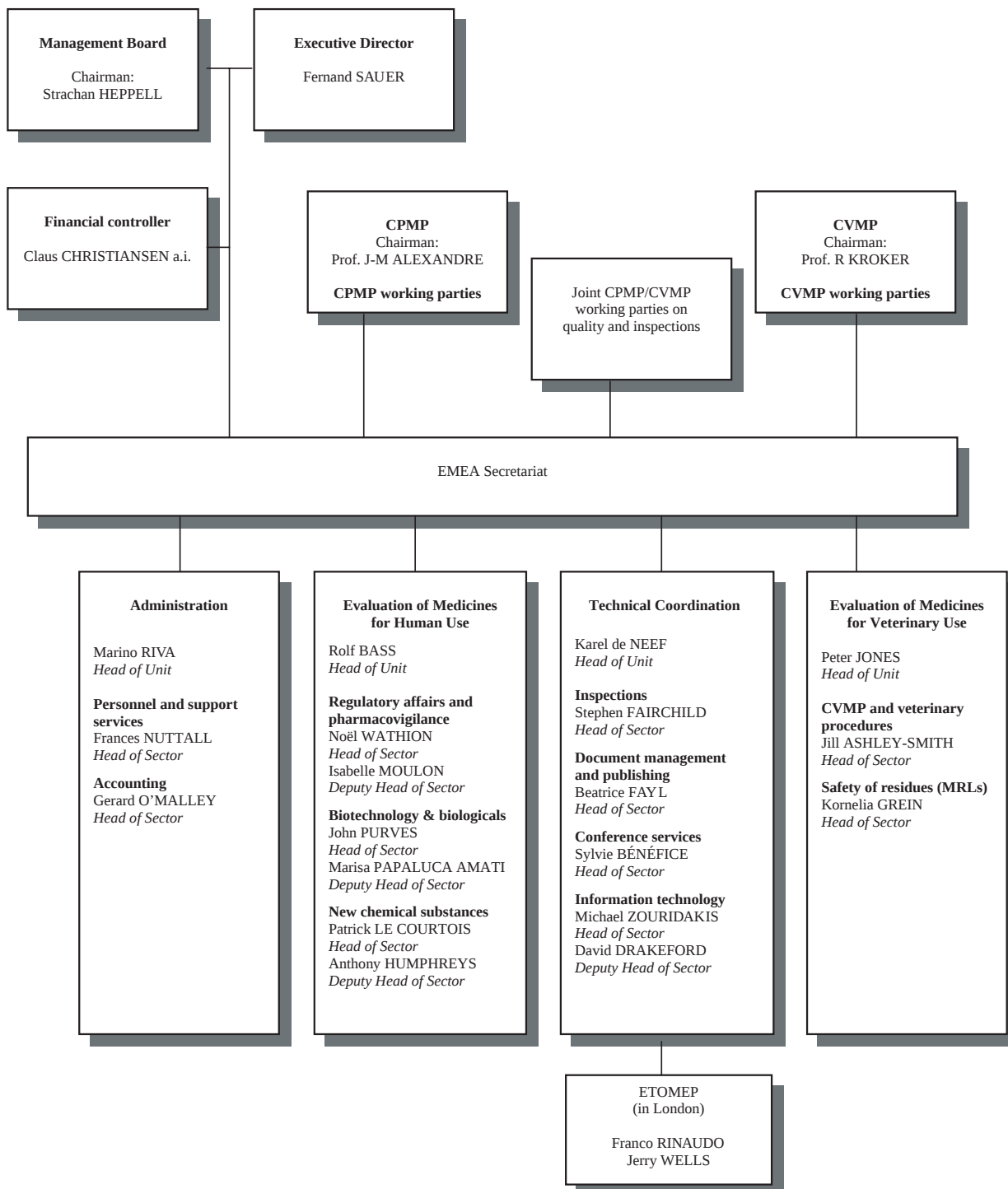
The European authorisation system is a single system made up of two procedures – the centralised and the mutual recognition procedures. The EMEA Management Board invited heads of national authorities to participate in its June meeting to look at global issues facing the European authorisation system. Similarly the EMEA now participates in meetings of heads of agencies. I welcome these positive developments and am grateful for their support, particularly as we prepare for the review of the European system in the year 2001.

The reform of fees at the end of 1998 is a major turning point for the Agency. With the help of the European Commission, the EMEA now has in place a mechanism that should allow it face the future with greater certainty. We remain committed to continuing our attempts to identify and optimise costs, and better coordinate work programmes with the European Commission in the interests of the European Union.

The Agency's staff have continued to make enormous efforts throughout 1998 despite freezes on recruitment and increasing workloads. An important contribution was that more than half the staff participated in the practical implementation of the quality management initiative. The EMEA is only one element in the European authorisation system and I was pleased to note growing interest from national authorities to join this initiative. The benefits to the European system in ensuring the best service for public and animal health are obvious. It is also important in the context of any future benchmarking exercise with other internationally recognised regulatory bodies.

Information to patients, health professionals and the public continued to be improved during 1998, in particular with the launch of the improved Internet site in 1998 giving access to a better range of documents and languages (<http://www.eudra.org/emea.html>). This is part of the Agency's efforts, as a multi-cultural EU organisation, to meet the needs of all partners.

ORGANIGRAM OF THE EMEA



1. EMEA IN 1998



Strachan Heppell

Romano Marabelli

1.1. The Management Board in 1998

Meetings of the Board in 1998

The Management Board met four times in 1998. The main business of the Board was dealt with in its 19 February, 30 September and 2 December meetings. For the first time those heads of national authorities not already members of the Board were invited to the 3 June brainstorming meeting. As in previous years this meeting concentrated on wider issues of concern to the whole European marketing authorisation system, including the future review of the system in 2001.

One of the first matters addressed by the Board was the adoption of the work programme for 1998-99 (see Annex 8 for publication details). Building on previous programmes, the document set clearer objectives for each operational sector of the Agency and reinforced links to resources. Importantly, the Board also acknowledged the contribution of national competent authorities in the operation of the centralised authorisation system.

The outcome of the workshop on a medical information network for Europe (MINE) held at the EMEA on 10 July 1998 was considered by the Board at its September meeting. The improvement of information for users of medicines and health professionals is one of the priority tasks of the EMEA. The Board therefore agreed to consider the development of a pilot project between the Agency, the European Commission Directorate-General for Industry and the Joint Research Centre. This would concern the electronic publication of the summary of product characteristics for products authorised after evaluation by the EMEA and also the mutual recognition procedure.

Pending the expected adoption by Council of certain amendments to the financial provisions of Regulation (EEC) No 2309/93, the Board agreed to consult the European Court of Auditors on the introduction of modifications in the EMEA internal financial regulation to allow for a financial reserve (see Annex 8).

Other matters addressed by the Board included herbal medicines and further measures towards transparency.

Budgetary decisions

The uncertainties of the Agency's financial perspectives in 1998 – mainly due to delays in the introduction of the fee reform – meant that the Board's main

1.1. The Management Board in 1998

1.2. The EMEA and its partners

1.3. Transparency, openness and quality management initiatives

1.4. International aspects

business focused on budgetary matters. Summaries of the Agency's budgets for 1996 to 1998 are presented in Annex 5.

Following the opinion of the European Court of Auditors, the Board granted discharge to the Executive Director in relation to the execution of the 1997 budget at its 2 December 1998 meeting. Discharge was also given to the accounting officer.

The 1998 budget total of ECU 31.9 million, adopted by the Board on 3 December 1997, remained unchanged, although a number of internal budgetary transfers of appropriations and two supplementary and amending budgets were adopted during the year.

The two budgetary adjustments were necessary primarily due to the delay in the fee reform. In particular the Board requested an additional ECU 2 million from the European Union budgetary authority to compensate for shortfall in forecast fee revenue, which was granted at the end of 1998.

The budget for 1999 of ECU 41.35 million was adopted by the Board at its 2 December meeting. The Community contribution initially requested was reduced by ECU 1 million to ECU 13 million, compensated for by additional revenue from fees and administrative charges.

After difficult discussions in European Parliament and Council, the EMEA welcomed the adoption of the new regulation on 14 December 1998. Council Regulation (EC) No 2743/98 came into force on 21 December 1998 (OJ L 345, 19.12.1998, p. 3).

The new regulation introduces two main changes, an annual fee and a fee for scientific advice given by the scientific committees. The level of some other fees has been adjusted and a number of modifications made. The new fee regime will allow the Agency a stable funding mechanism in the future. The European Parliament has indicated that it wishes to look at the regulation again in 2001, including further data from the EMEA and national authorities on the costs associated with the operation of the European procedures.

Financial control

Pending adoption by the European Parliament and Council of proposals for the transfer of financial control responsibilities of all EU bodies to the European Commission, the Agency's interim financial controller, Claus Christiansen, continued in post during 1998, together with an assistant. The adoption of these proposals is expected in early 1999 and close contacts were maintained with the European Commission Directorate-General for Financial Control to ensure a smooth transfer.

The quality of transactions continued to improve, with the number of transactions revised for procedural, or in a small number of cases material errors, falling to approximately 2 % by the end of the year. In line with internal targets, most transactions presented for approval to financial control were dealt with within five days, with three-quarters of all requests being dealt with within two days.

1.2. The EMEA and its partners

European institutions

The Agency's activities touch an increasingly large number of areas of European Union competence. This has brought the EMEA into contact with almost half of the Commission's operational Directorates-General. The Agency's principal contact remains with the Directorate-General for Industry and in particular the Unit for Pharmaceuticals and Cosmetics (DG III/E/3).

Contacts with European Commission Directorates-General:

DG I and DG IA - External relations
DG III - Industry
DG V - Employment, Industrial Relations and Social Affairs
DG VI - Agriculture
DG IX - Personnel and Administration
DG XII - Science, Research and Development
Joint Research Centre
DG XIX - Budgets
DG XX - Financial Control
DG XXIV - Consumer Policy and Consumer Health Protection



During 1998, the EMEA participated at all meetings of the pharmaceutical committees for human and veterinary medicines, together with relevant working group meetings. This is the Commission's main policy body composed of Member State representatives and is chaired by DG III. The EMEA also participated at a number of meetings of the DG XXIV scientific committees and representatives of DG XXIV were also invited to attend meetings of the CPMP and CVMP.

The European Parliament continued to support the work of the EMEA, in particular through its Committee on Environment, Consumer Protection and Public Health, chaired by Mr Kenneth Collins. A number of important legislative proposals of relevance to the Agency were considered by Parliament during 1998. The EMEA worked closely with the relevant committees, in particular the Committee for Budgets, Committee for Research, Technological Development and Energy and Committee for Budgetary Control. The EMEA also attended meetings of the informal European Parliament Intergroup on Pharmaceuticals, chaired by Professor Umberto Scapagnini.

The Agency was pleased to offer its facilities for a meeting of the Single Market Observatory of the European Union Economic and Social Committee in May.

A meeting of the European Group on Ethics in Science and New Technologies was also hosted at the EMEA in June 1998. Formerly the Group of Advisers on the Ethical Implications of Biotechnology, the task of the Group is to advise the European Commission on all ethical questions relating to science and new technologies. At their meeting, the Group prepared an opinion on the ethical aspects of human tissue banking that was submitted to the European Commission in July, including a role for the EMEA in a coordinated European approach to handling this issue.

Contact with other EU decentralised bodies was increased through participation by the EMEA with the European Monitoring Centre for Drugs and Drug Addiction in the development of a guideline on risk assessment of new synthetic drugs.

Cooperation with the European Pharmacopoeia continued in 1998 with the EMEA participating as part of the EU delegation and observers from the Pharmacopoeia Secretariat attending a number of EMEA working party meetings. Further details are given in Chapter 4.

National competent authorities and interested parties

The support and contribution of national authorities to the Agency continues to be strong. In particular the EMEA now has access to some 2 200 experts nominated by the national authorities. The evaluation, surveillance and inspection activities of the EMEA are carried out by these experts under contracts for service, for which payment is made by the EMEA from the fees paid by applicants. This contract is part of the 'Statement of principles' document adopted by the Management Board in December 1996 (see Annex 8 for details).

The increasing importance of the partnership between national authorities and the EMEA has led to an increasing number of briefing and exchange visits between officials from national authorities and the EMEA on a broad range of subjects. Meetings in 1998 were held with representatives of authorities from Belgium, Germany, France, Austria, Sweden and UK. In addition to Members of the European Parliament, the EMEA also received delegations from the Belgian, Italian and UK parliaments.

At the same time, national authorities continued to take advantage of the possibility to second officials for short periods of time to the EMEA. In 1998 the Agency was able to welcome national experts from Denmark, Germany, France and Italy.

Regular quarterly meetings with principal interested parties continued to be held in 1998, together with members of the EMEA scientific committees. As in previous years the Agency also co-hosted a number of successful Info-days with representative organisations from the animal and human health industry. Technical workshops were also held on a number of specific topics, including pre-submission guidance, submission of variation applications, issuing of certificates for medicinal products and European public assessment reports.

As interest groups become increasingly better organised at a European level, the EMEA has sought to widen the scope of interested parties and learned societies with which it has contacts. The Agency's efforts to increase transparency and communication are appreciated by these groups, who have shown themselves interested in increasing contacts with the EMEA.

Interested parties invited to CPMP quarterly meetings:

- Bureau Européen des Unions de Consommateurs (BEUC)
- European Federation of Pharmaceutical Industries' Associations (EFPIA)
- Association Européenne des Spécialités Pharmaceutiques Grand Public (AESGP)
- European Generic manufacturers' Association (EGA)
- Standing Committee of European Doctors
- Groupement des Pharmaciens de l'Union Européenne (GPUE)

Interested parties invited to CVMP quarterly meetings:

- Bureau Européen des Unions de Consommateurs (BEUC)
- Fédération de la Santé Animale (FEDESA)
- Committee of Agricultural Organisations in the EU/
General Committee of Agricultural Cooperation in the EU (COPA-COGECA)
- Groupement des Pharmaciens de l'Union Européenne (GPUE)
- Federation of Veterinarians in Europe (FVE)

Other groups that participated in EMEA meetings in 1998 include:

- Dansk Farmaceutforening (Danish Pharmacists' Association)
- Drug Information Association (DIA)
- European Association of Genetic Support Groups (EAGS)
- European Chemical Industry Council (CEFIC)
- Health Action International (HAI)
- International Federation of Associations of Pharmaceutical Physicians (IFAPP)
- International Society of Drug Bulletins (ISDB)
- Irish Pharmaceutical and Chemical Manufacturers Federation (IPCMF)
- Pan-European Federation of Regulatory Affairs Societies (PEFRAS)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- Verband Forschender Arzneimittelhersteller (VFA)

1.3. Transparency, openness and quality management initiatives

Transparency and openness

The use of Internet technology to give the widest possible access to documents of the EMEA is an important aspect of the Agency's work. A new website was launched in September 1998 with an improved structure that will in particular allow for better access to documents in different languages. The Internet address remains the same (<http://www.eudra.org/emea.html>).

Together with the new website, and further to the Executive Director's decision on rules on access to documents of 3 December 1997, a pilot catalogue of public documents was also published in September. Work continued in 1998 on producing a more interactive tool to allow searching and direct access to public documents through the Internet.

Public access to the list of European experts nominated by Member States and their declarations of interests has been available for public consultation at the EMEA since 1995. After consultation with the scientific committees, the Management Board gave its approval in December 1998 to the publication of the list of names. It is intended to have completed preparation by early 1999.

At its September meeting, the Management Board endorsed a proposal for a policy on communication of information during the evaluation of applications made to the Agency and after the adoption of an opinion by the scientific committees (EMEA/MB/011/98-Rev.1). One aspect of this, statistics on the withdrawal of applications, is now reported on in Chapters 2 and 3 of this report.

As a matter of principle, details of applications submitted to the EMEA remain confidential. The Board however also agreed to the release of information by the Agency during the evaluation phase in exceptional circumstances. In particular release of information could be justified when detailed information is already in the public domain, or where misleading information in the public domain could be corrected by means of a factual statement.

The release of some information after adoption of the scientific committees' opinions was in principle accepted after the opinion has become final and only once the European Commission and Member States have been informed. In practice this will be 60 days after the adoption of the opinion.

Quality management initiatives

The quality management initiative begun in 1997 began to show tangible results during 1998. The nine teams looking at different aspects of the Agency's activities presented the initial result of their work at a general assembly of all staff in July 1998. Members of the Management Board and scientific committees were able to see the result of the teams' work in a display arranged near to the meeting rooms at the EMEA.

The teams tackled a number of important topics, including the Agency's business planning, management of information, scientific opinions and scientific advice, quality of product information, internal auditing, provision of internal performance indicators, relationship with the Agency's different partners, staff training and appraisal, and also implementation of management decisions.

While some projects were concluded during the course of the year, the process of ensuring quality management is necessarily a continuous one. A manual on quality management at the EMEA was produced to help staff in their work and internal auditing procedures were put in place towards the end of 1998 to ensure that the progress made is continued in future.

The EMEA recognises that it is only one element in the European authorisation system and has sought to encourage national competent authorities to join in the quality management initiative. This is particularly important in the context of any future benchmarking exercise with other internationally recognised regulatory bodies.

1.4. International aspects

Although constrained by funding, the EMEA's role in supporting the European Commission in international relations continued in 1998.

The European Economic Area Joint Committee decision to allow the participation of Iceland and Norway in the work of the EMEA was postponed until the beginning of 1999. Pending the entry into force of the decision, an exchange of letters was entered into between the EMEA with Iceland and Norway that allowed them to participate as observers to the Management Board, scientific committees and working parties.

The EMEA continued to participate in the International Conferences for Harmonisation for human and veterinary medicines (ICH and VICH). This on-going process of harmonisation between the regulatory authorities and industry representatives of the EU, Japan and the US progressed in 1998. Within the ICH, 37 trilateral positions have now been completed for human medicines, details of activities in 1998 are given in Chapter 2. Progress was also made in the veterinary medicines sector and details of the VICH process are given in Chapter 3.

Within the context of the Agency's technical support to national authorities of central and eastern European countries, observers from the Cadreac group (Collaboration agreement of drug regulatory authorities in European Union associated countries) continued to attend meetings of a number of working parties of the scientific committees. Discussion also continued on a procedure

for the exchange of assessment reports and safety information on authorised medicinal products. A trainee from Estonia began an internship with the EMEA at the end of 1998.

The EMEA continued to receive information visits from national authorities of a number of non-EU countries. Visits in 1998 included representatives from Bosnia and Herzegovina, Canada, China, Cuba, Hong Kong, Japan, Nigeria, Poland, Thailand, United States and Zimbabwe.

Cooperation with the World Health Organisation continued and in particular the EMEA participated in an international training course on the registration of medicines held in Tunisia in September 1998.

As in previous years the EMEA was able to offer its facilities to host the annual meetings of both the International Grains Council and International Sugar Organisation, both international organisations whose seats are also in Canary Wharf, London.

2. MEDICINAL PRODUCTS FOR HUMAN USE

2.1. Unit for the Evaluation of Medicinal Products for Human Use

Within the Unit, Professor Josep Torrent-Farnell, Head of Sector for new chemical substances left the EMEA in 1998 to become director of the Spanish Medicines Agency and was succeeded by Dr Patrick Le Courtois. The other Heads of Sector, Mr Noël Wathion and Dr John Purves, continued in place under the Head of Unit, Professor Rolf Bass. At the end of 1998, Dr Isabelle Moulon, Dr Marisa Papaluca Amati and Mr Anthony Humphreys were named as Deputy Heads of Sector.

The Unit invested in new initiatives, including quality management, the application tracking system and the product information quality project. While this placed a strain on available staff, it will in the medium term result in improvements in productivity. Other initiatives included management and language training for staff.

In the second half of 1998 the number of meetings was reduced due to a contingency plan and planned recruitment was delayed.

The number of new centralised applications received during 1998 is comparable to the previous year, whereas the workload arising from the maintenance of centralised marketing authorisations increased significantly. The number of type I variations also increased noticeably, whereas the number of type II variations remained stable. Processing timelines, which are the key performance indicators for centralised procedures, were met for all applications.

The organisation and content of the scientific review process have been the subject of discussions at plenary and informal CPMP meetings.

2.1. Unit for the Evaluation of Medicinal Products for Human Use

2.2. Operation of the CPMP

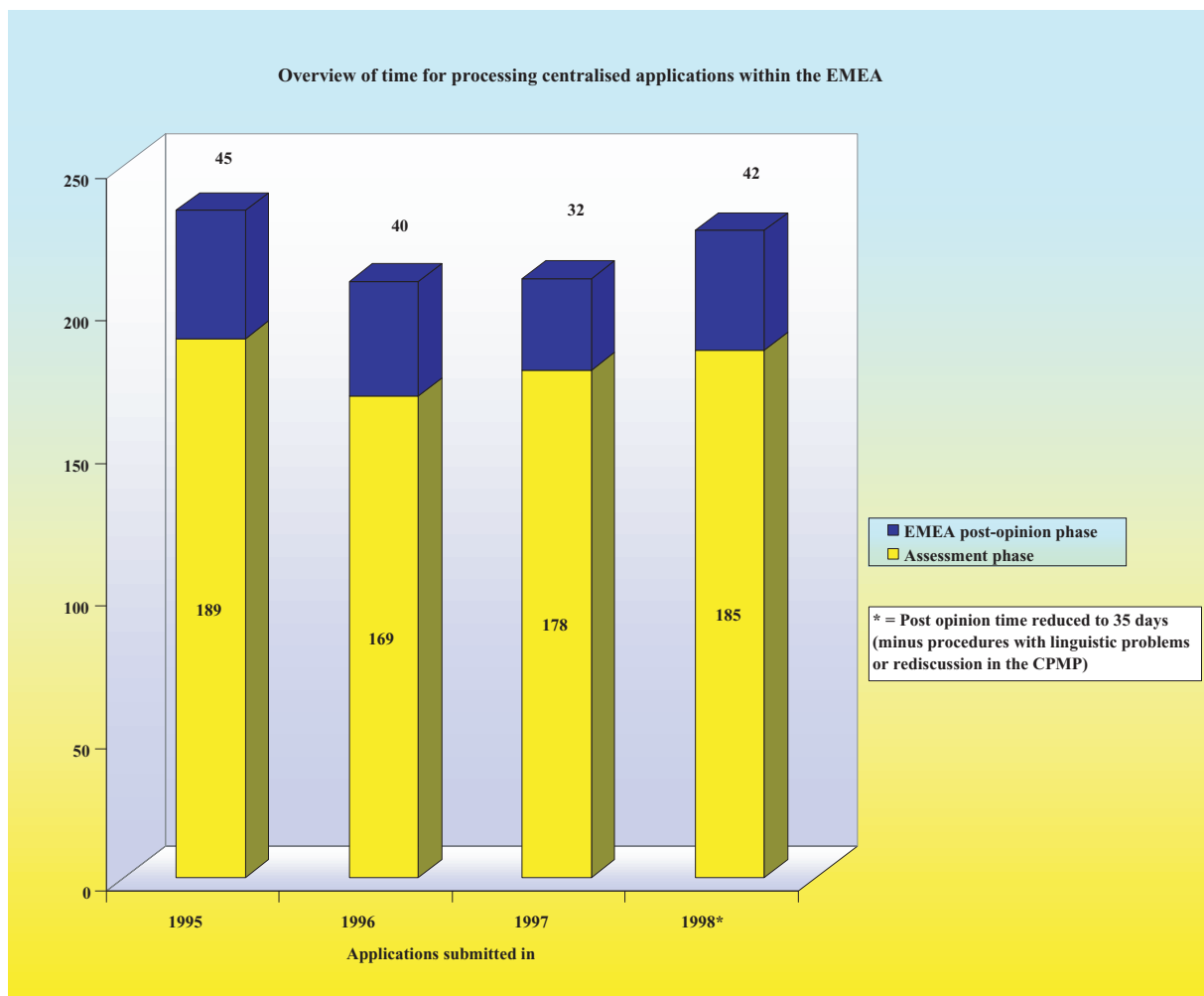
2.3. Other CPMP activities

2.4. CPMP working parties

2.5. Ad hoc EMEA working group on herbal medicinal products

2.6. Mutual recognition of medicinal products for human use

Continued improvements to the European public assessment report are necessary to make the scientific basis of CPMP opinions more transparent, in addition to improving the quality of summary of product characteristics and patient leaflets.



The number of occasions on which scientific advice was sought and provided increased in 1998, resulting in an increase in workload for both the Committee for Proprietary Medicinal Products and Unit.

The centralised procedure usually deals with highly innovative medicinal products, either biotechnological compounds or new active substances. By their nature these compounds may be either completely novel in their mode of action or are new treatments for use in serious diseases where current therapies are of limited success. A number of products were authorised under exceptional circumstances with follow-up measures required by the CPMP. Pharmacovigilance is of especial importance to ensure that unexpected side effects are recognised rapidly and appropriate warnings given quickly to health professionals and patients.

The EMEA was also concerned in the development of medicines for use in children, improved product information for anti-microbial agents ('antibiotics') and the use of materials of animal origin in the manufacture of medicines.

2.2. Operation of the CPMP

In January 1998 nominations for CPMP members were made for the second three-year term of the CPMP (1998-2000). There were five new members; all the other members stayed on for the second term (see Annex 2 for details). Professor Jean-Michel Alexandre was re-elected Chairman and Dr Mary Teeling was elected Vice-Chairman of the CPMP for the period 1998-2000.



Jean-Michel Alexandre

The CPMP noted with great sadness the death on 30 September 1998 of Dr Susan Wood, one of the UK CPMP members and chairman of the CPMP Pharmacovigilance Working Party. On the occasion of its October plenary meeting, the CPMP paid tribute to her achievements and outstanding contribution to public health internationally.

As of June 1998, a new structure and organisation of CPMP meetings was introduced: CPMP plenary meetings start on Tuesday of the CPMP week and continue until Thursday. Scientific advice meetings as well as meetings of the Mutual Recognition Facilitation Group (MRFG) are scheduled for the Monday, thus avoiding any overlapping of venues and generating availability of experts.



Mary Teeling

Applications and opinions

Centralised procedures	1996	1997	1998	Total 1995-98
Applications received				
Part A	12	20	12	177
Part B	23	40	33	
Withdrawals	4	5	19	30
Opinions adopted by product				
Part A	14	6	11	103*
Part B	15	19	30	
Opinions adopted by substance				
Part A	11	6	11	80*
Part B	12	13	19	
Type I variations				
Part A	14	57	50	294
Part B	13	52	108	
Type II variations				
Part A	3	19	26	130
Part B	13	28	40	
Extension & abridged applications				
Part A	3	32	11	54
Part B	2	2	4	

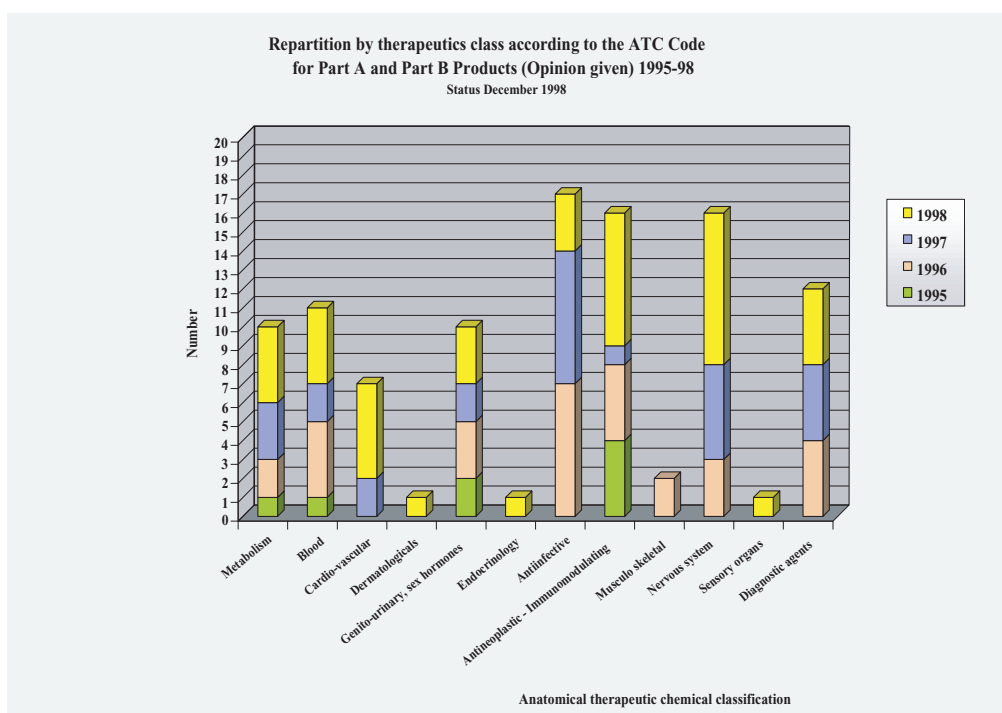
* These figures include negative opinions given for three products, representing two substances.

Confirming the trend established since the launch of the EMEA, two-thirds of applications in 1998 continued to be optional, where the applicant had the choice of procedures under Part B of the Annex to Council Regulation (EEC) No 2309/93. A total of 12 applications were made for biotechnology medicinal products falling under Part A of the Annex and 33 applications for innovative medicines falling under Part B.

Following a new European Commission policy requiring extensive justification for any multiple applications, the number of such applications fell compared to previous years.

In 1998, 38 positive opinions for medicinal products were adopted. Detailed information on positive opinions granted in 1998 and community authorisation decisions, as approved by the Commission in 1998, are given in Annex 6.

The type of medicinal products for which opinions have been given by the CPMP has evolved since 1995 and now covers all major therapeutic classes.



The majority of positive opinions were based on active control studies where the benefits and risks of the new product are compared with already authorised products. In some cases comparison with placebo can be accepted instead, for example, where a comparator product was not available because of the innovative character of the product.

In 1998, three negative opinions, by a majority of votes, were given by the CPMP concerning two active substances. Two negative opinions related to two medicinal products containing the same new active substance (Part B), a nervous system drug, propentofylline. The other negative opinion related to a medicinal product containing a new active substance (Part A), an antithrombotic agent, saruplase.

Variations

During 1998, 158 type I and 66 type II variations were processed. Negative opinions were given by the CPMP concerning two type II variations for medicinal products containing the same active substance (Part B, an antineoplastic agent, topotecan) relating to an extension of the indications.

Withdrawals prior to opinion

Withdrawal of applications in the centralised procedure is possible before the CPMP issues an opinion. This opportunity is often taken by applicants to avoid a possible negative opinion. In 1998, 19 applications were withdrawn voluntarily by applicants; seven applications for products falling within the scope of Part A of the Annex to Council Regulation (EEC) No 2309/93 and 12 Part B products.

From 1995 to 1998 a total of 30 applications were withdrawn. Four procedures concerned converted 'ex-concertation procedures' and 26 concerned new centralised applications. Most withdrawals were linked to specific clinical problems that might have led to negative benefit-risk assessment by the CPMP. Withdrawals in 22 instances were due to lack of clinical efficacy or safety issues, two were due to quality and manufacturing issues and one due to the lack of validity of data.

Some of the withdrawn procedures were analysed in 1998. It should be noted that for none of these procedures CPMP scientific advice had been requested. Most of the withdrawals appear to be due to premature applications, with applicants unable to provide adequate additional information, data and responses even within a longer clock stop.

Rapporteurs

Rapporteurs and co-rapporteurs were appointed for applications representing 32 active substances in 1998. An even distribution between members was ensured by requiring applicants to propose three or four alternatives.

Delegates' origin	Rapporteur		Co-rapporteur		Total
	Part A	Part B	Part A	Part B	
Belgique/België	0	2	1	1	4
Danmark	1	0	1	1	3
Deutschland	2	1	2	3	8
ΕΛΛΑΔΑ/Greece	0	0	0	0	0
España	0	4	1	0	5
France	2	4	0	3	9
Ireland	0	3	0	1	4
Italia	0	1	0	2	3
Luxembourg	0	0	0	1	1
Nederland	1	2	0	4	7
Österreich	0	0	0	1	1
Portugal	0	1	0	0	1
Suomi/Finland	0	2	0	1	3
Sverige	1	3	1	5	10
United Kingdom	1	1	2	1	5
Total	8	24	8	24	64

Operational matters

The Unit continued its efforts in 1998 to provide legal, regulatory and procedural advice to the CPMP, its working parties and the applicants. In particular this was through increased development of standard operating procedures and the organisation of 70 pre-submission meetings. An EMEA pre-submission guidance for users of the centralised procedure (EMA/H/38179/1998) was made available in November 1998 to provide further assistance.

In accordance with the Commission communication on the Community marketing authorisation procedures for medicinal products, (OJ C 229, 22.7.1998, p. 4) the EMEA developed a procedure for notifications of parallel distribution of centrally authorised products. The procedure came into force on 20 November 1998 and outlines the steps which parallel distributors for centrally authorised products should follow. Some 258 notifications were received in 1998.

The following guidance documents were adopted by the CPMP:

Reference number	Title	Status
CPMP/040/98	Position paper on voting in the framework of the discussion and adoption of CPMP opinions	Adopted in March 1998
EMEA/SOP/001/97	Standard operating procedure on referrals in accordance with the provisions of Council Directive 75/319/EEC in the case of safety concerns related to medicinal products marketed in the European Union	Adopted in April 1998
EMEA/SOP/H/001/98	Standard operating procedure on the release of assessment reports to applicants/marketing authorisation holders	Adopted in October 1998
CPMP/328/98	Guidance paper on the acceptability of trade names for medicinal products processed through the centralised procedure	Released for consultation in April 1998

2.3. Other CPMP activities

Scientific advice

Scientific advice is the opportunity to address unclear developmental issues with the CPMP before submission of an application for a marketing authorisation.

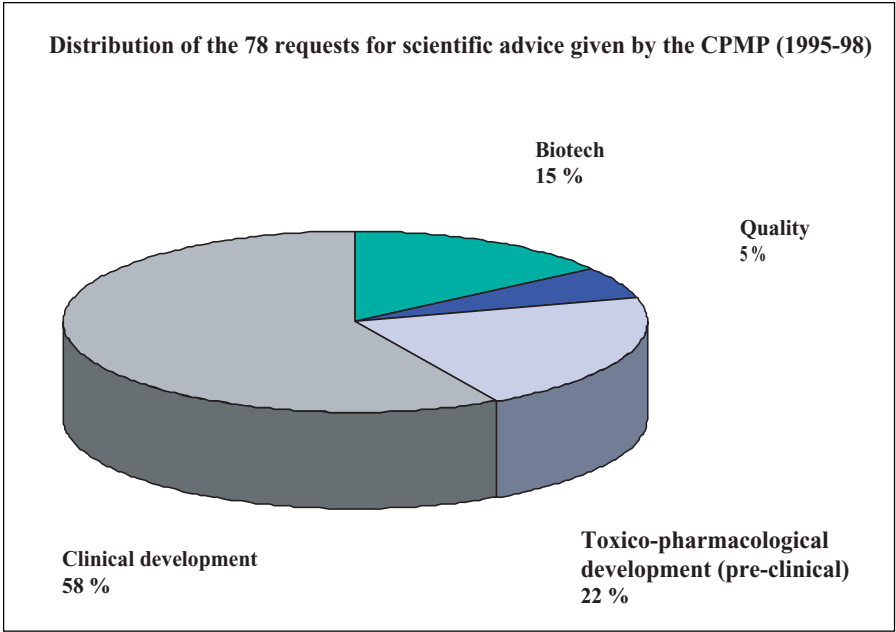
The number of times on which scientific advice was given in 1998 increased significantly, as industry has recognised the added value given by the CPMP in the early stages of development of their medicinal products. Although the number of requests and follow-up to the initial requests increased dramatically compared to 1996 and 1997, the average length of the procedure remained at three months. In 1998 the three first marketing authorisation applications following the provision of EMEA scientific advice were submitted through the centralised procedure. Opinions for these applications are still awaited.

In order to improve the handling of the increased workload, further measures were implemented. This action led to a strengthening of the scientific advice procedure by creating a network of experts, a closer involvement of the CPMP working parties and a reinforcement of the support from the EMEA Secretariat.

In order to improve the procedure for the provision of scientific advice, expert meetings are held to enable in-depth discussions on specific scientific issues relating to the different requests. A new step in the scientific advice procedure is the provision of a list of specific issues to the applicant that are to be addressed by the latter during the oral presentation to the CPMP consultation group, where appropriate. This allows a more focused discussion and hence improves the quality of scientific advice.

Details on the provision of scientific advice for 1998 are given below:

Requests submitted to CPMP	Advice given	No advice given	Oral consultations
52 (42 + 10 follow-up)	43 (35 + 8 follow-up)	3 (1 + 2 follow-up)	16



Referrals

Public health concerns in relation to nationally authorised products, may be referred to the EMEA both within the framework of the mutual recognition procedure and for safety concerns for other products.

A referral initiated in 1997 under Article 12 of Council Directive 75/319/EEC concerning the arrhythmogenicity of medicinal products containing terfenadine, a non-sedating antihistamine, was finalised in 1998. The procedure involved 80 marketing authorisation holders. All 83 marketing authorisations for terfenadine 120 mg tablet formulations and terfenadine 60 mg + pseudoephedrine HCl 120 mg tablet formulations were withdrawn. In addition variations were introduced to all 139 marketing authorisations and amendments made to the summary of product characteristics for all terfenadine 30 mg tablet, 60 mg tablet and 6 mg/ml oral suspension formulations (OJ C 331, 29.10.1998, p. 5).

A referral initiated in 1997 under Article 7(5) of Commission Regulation (EC) No 541/95 concerning a type II variation for a biotechnological medicinal product containing epoetinum alfa, authorised under the ‘ex-concertation procedure’, was finalised in 1998. The referral related to an application to introduce an additional indication for the use of the products to reduce exposure to allogeneic blood transfusions prior to elective orthopaedic surgery. The additional indication was approved by the CPMP.

Type of referral	Date of CPMP final opinion	International non-proprietary name (INN)
National authorisations		
Article 12 Council Directive 75/319/EEC	25 February 1998 Procedure ongoing	Terfenadine Vigabatrin
Article 15 Council Directive 75/319/EEC	Procedure ongoing	Dexfenfluramine; Fenfluramine Phentermine; Amphetamine
	Procedure ongoing	Clobenzorex; Fenbutrazate; Fenproporex; Mazindol; Mefenorex; Norpseudoephedrine; Phenmetrazine; Phendimetrazine; Propylhexedrine
	Procedure ongoing	
Mutual recognitions concertation procedure		
Article 7(5) Commission Regulation (EC) No 541/95	25 February 1998 Procedure ongoing Procedure ongoing	Epoetinum alfa Interferon alpha 2a Molgramostim
Article 10 Council Directive 75/319/EEC	Procedure ongoing	Tirofiban
Article 15 Council Directive 75/319/EEC	Procedure ongoing	Sertindole

2.4. CPMP working parties

The CPMP working parties concerning pharmacovigilance, biotechnology, efficacy and safety, as well as the joint CPMP/CVMP Quality Working Party continued to meet regularly in the first half of 1998, although less often in the second half due to contingency measures.

They continued to provide recommendations to the CPMP, mainly in the form of position papers, points to consider, notes for guidance and CPMP/ICH guidelines. Furthermore, new concept papers were adopted by the CPMP as a starting point for the future development of notes for guidance.

CPMP position statements/position papers are scientific statements aimed at communicating the current state-of-the-art EU-wide scientific position on a specific topic.

EMA documents

Concept papers are intended to address specific issues in any stage of the development of medicinal products within CPMP working parties or ad hoc working groups with a view to laying down the foundation for future guidance, either as points to consider documents or as notes for guidance.

Documents entitled 'Points to consider' express the view of the CPMP in an area of medicinal product development where limited experience is available and knowledge is evolving fast. These documents need to be flexible and easily updated to reflect progress.

Notes for guidance – sometimes also called guidelines – are documents aimed at:

- (a) providing a basis for practical harmonisation of the way in which Member States and EMA interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy (analytical, pharmacotoxicological and clinical standards and protocols in respect of testing of medicinal products, Annex to Council Directive 75/318/EEC); and
- (b) facilitating the preparation of applications for marketing authorisations.

A standard operating procedure (SOP) provides clarification to regulatory authorities and applicants on implementation of EU pharmaceutical legislation.

The CPMP, its working parties and experts continued to give major input to the ICH process preparing the EU position. Considerable progress was made with several guideline documents being finalised. Documents signed off by the ICH Steering Committee included those on the duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing, ICH topic S4) and choice of control group in the clinical trials (ICH topic E10).

Concerning the common technical document, great progress has been made for the pre-clinical part particularly on the harmonisation of the table of contents. For the efficacy and clinical safety part, the scope of harmonisation for the table of contents for study reports and tabulated listing of studies was agreed during the ICH meeting in Tokyo, which was held in September 1998. A workshop of clinical assessors from all CPMP delegations chaired by Dr Barbara van Zwieten-Boot was held in order to prepare the EU position on the efficacy and clinical safety part for the September 1998 Tokyo meeting.

Highlights from each working party and the status of documents prepared in 1998 are given below. Guidelines relating to pharmaceutical quality are presented in Chapter 4.

Pharmacovigilance activities and the Pharmacovigilance Working Party

The Pharmacovigilance Working Party (PhVWP) chaired by Dr Susan Wood (†) held seven meetings in 1998. The working group considered 19 issues at the request of the CPMP and 39 issues at the request of the Member States.

The Pharmacovigilance Working Party continued to review safety concerns in relation to centrally and nationally authorised medicinal products. In this respect a core European warning concerning driving and operation of machinery when using insulin was agreed upon by the working party and endorsed by the CPMP.

One document dealing with operational matters was agreed and subsequently adopted by the CPMP. 'Principles of providing the World Health Organisation with pharmacovigilance information' was adopted in January 1998 (CPMP/PhV/053/98). It will be included in Volume IX of 'The rules governing medicinal products in the European Union' (see Annex 8 for publication details).

In 1998 the EMEA was notified of an increasing number of reports of suspected serious unexpected adverse drug reactions occurring outside the EU for centrally authorised products. Some 4 417 such reports were received in 1998. A total of 4 516 reports of serious adverse drug reactions which occurred within the EU were received.

In order to prevent potential precipitation of the active substance in Norvir, changes to the storage recommendations and shelf-life were recommended. This was followed up by a type II variation procedure.

The Community marketing authorisation for Tasmar (tolcapone), originally authorised for adjunctive treatment of Parkinson's disease, was suspended because it became apparent that its benefits did not outweigh the risks of use. Concerns over Comtess (entacapone), which has a similar mode of action to tolcapone, also led to introduction of different warnings. Mabthera (rituximab), authorised for the treatment of certain forms of lymphoma, was also subject to increased restrictions on use. In each case, a public statement was issued by the EMEA and made available on the Agency's website.

Biotechnology Working Party

The Biotechnology Working Party (BWP), chaired by Professor Giuseppe Vicari, met on eight occasions in 1998. During this year, the BWP has continued to provide specialist technical assistance to the CPMP on applications submitted to the EMEA. General advice has also been given on the manufacture and control of biotechnological and biological medicinal products, including products derived from blood and plasma, and of immunological products.

In the light of the emerging information, a workshop of international experts on transmissible spongiform encephalopathies (TSEs), convened under the auspices of the CPMP, was held on 15 January 1998 to consider the available information on new variant Creutzfeldt-Jakob disease (nv-CJD) and relevant TSEs. The CPMP adopted a position statement on nv-CJD and plasma-derived medicinal products on 25 February 1998 (CPMP/201/98), which included recommendations on the action to be taken in relationship to medicinal products,

if donations were subsequently found to be from patients with nv-CJD.

In addition, the BWP proposed a revision of the CPMP note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products, which was released for consultation. The recommendations (adopted in December 1997) for the production of tallow derivatives for use in pharmaceuticals (CPMP/BWP/1163/97), as well as the recommendations for gelatine use in pharmaceuticals, were incorporated into the proposed revision of the 'TSE guideline'. In this area, the CPMP also endorsed the need to hold a workshop between CPMP/BWP and other interested parties to share the available information on the progress on assays for markers of TSE in relation to their potential applications to medicinal products.

The first EMEA workshop on gene therapy was held on 23 April 1998. The objective of this workshop was to identify priorities, to facilitate the progress of new and promising therapeutic strategies and revise gene therapy guidelines. Participants of the workshop included representatives of the European Parliament, European Commission and members and experts of the CPMP, as well as representatives from industry, academia and patient groups. The EMEA provided a forum for the exchange of scientific information and the debate was the basis for the ongoing revision of gene therapy guidelines.

At the request of the Mutual Recognition Facilitation Group, the Biotechnology Working Party has provided scientific advice relating to the selection of virus strains for incorporation into influenza vaccines. The recommendation for influenza strains, for use in influenza vaccine production in Europe, was reached by consensus of opinion of the experts attending the ad hoc Influenza Working Group in conjunction with the Biotechnology Working Party.

The following documents were adopted or released for consultation by the CPMP in 1998:

Reference number	Guidelines	Status
CPMP/BWP/201/98	New variant CJD and plasma-derived medicinal products	Adopted in February 1998
CPMP/BWP/921/98	Report on selection of influenza vaccines strains for 1998/99	Adopted in May 1998
CPMP/BWP/972/98	Viral safety of oral poliovirus vaccine	Adopted in May 1998
CPMP/BWP/1952/98	Position statement on Polysorbate 80	Adopted in October 1998

Reference number	Guidelines	Status
CPMP/BWP/1106/97	Concept paper on gene therapy	Adopted in January 1998
CPMP/BWP/1113/98	Concept paper on the development of a CPMP guideline on comparability of biotechnology-derived products	Adopted in June 1998

Reference number	Guidelines	Status
CPMP/BWP/390/97	The introduction of nucleic acid amplification technology (NAT) for the detection of hepatitis C virus RNA in plasma pools (addendum to note for guidance on plasma-derived medicinal products)	Adopted in March 1998
CPMP/BWP/477/97	Pharmaceutical and biological aspects of combined vaccines	Adopted in July 1998
CPMP/BWP/269/95 rev.2	Note for guidance on plasma-derived medicinal products	Adopted in July 1998
CPMP/BWP/1230/98	Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products. Revision October 1998	Released for consultation in October 1998

Efficacy working party

The efficacy working party (EWP), chaired by Professor Alfred Hildebrandt and co-chaired by Dr Barbara van Zwieten-Boot met on five occasions in 1998 with a number of break-out and ad hoc meetings.

Cooperation with the other working parties continued, particularly with the Joint CPMP/CVMP quality working party on modified release oral and transdermal dosage form, with the joint group on kinetics and with the BWP on clinical investigation of new vaccines and gene therapy.

The EWP/QWP joint group on pharmacokinetics, chaired by Professor José Guimarães Morais, met six times and continued its task on updating the existing

note for guidance on bioavailability and bioequivalence, as well as on population pharmacokinetics (CPMP/EWP/QWP/1401/98).

The following documents were adopted or released for consultation by the CPMP in 1998:

Reference number	Points to consider	Status
CPMP/EWP/784/97	Clinical investigation of medicinal products used in the treatment of osteoarthritis	Adopted in July 1998
CPMP/EWP/556/98	Clinical investigation of slow-acting anti-rheumatic medicinal products in rheumatoid arthritis	Adopted in December 1998
CPMP/EWP/562/98	Clinical investigation of medicinal products in the treatment of patients with chronic obstructive pulmonary disease	Released for consultation in October 1998

Reference number	Concept papers	Status
CPMP/EWP/518/97	Clinical investigation of antidepressant agents medicinal products (revision)	Adopted in January 1998
CPMP/EWP/561/98	Clinical investigation of medicinal products for the treatment of multiple sclerosis	Adopted in April 1998
CPMP/EWP/567/98	Clinical investigation of medicinal products for the treatment of bipolar disorders	Adopted in April 1998
CPMP/EWP/560/98	Clinical investigation of medicinal products for the treatment of acute ischemic stroke	Adopted in April 1998
CPMP/EWP/566/98	Clinical investigation of medicinal products for the treatment of epileptic disorders (revision)	Adopted in April 1998
CPMP/EWP/571/98	Clinical investigation of medicinal products for the treatment of cardiac failure (revision)	Adopted in April 1998
CPMP/EWP/714/98	Clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (revision)	Adopted in April 1998

Reference number	Concept papers	Status
CPMP/EWP/570/98	Clinical investigation of medicinal products for the treatment of unstable coronary artery disease	Adopted in April 1998
CPMP/EWP/707/98	Clinical investigation of medicinal products for prophylactic treatment of peri- and post-operative venous thrombo-embolic risk	Adopted in April 1998
CPMP/EWP/563/98	Clinical investigation of medicinal products for treatment of venous thrombo-embolic disease	Adopted in April 1998
CPMP/EWP/559/98	Clinical investigation of medicinal products for prevention and treatment of osteoporosis in men	Adopted in April 1998
CPMP/EWP/565/98	Clinical investigation of medicinal products for treatment of amyotrophic lateral sclerosis	Adopted in July 1998
CPMP/EWP/1119/98	The evaluation of diagnostic agents	Adopted in July 1998

Reference number	Guidelines	Status
CPMP/EWP/559/95	Clinical investigation of medicinal products in the treatment of schizophrenia	Adopted in February 1998
CPMP/ICH/289/95 (E5)	Ethnic factors in the acceptability of foreign clinical data	Adopted in March 1998
CPMP/ICH/363/96 (E9)	Statistical principles for clinical trials	Adopted in March 1998
CPMP/EWP/563/95	Clinical investigation of medicinal products in the treatment of Parkinson's disease	Adopted in December 1998
CPMP/EWP/280/96	Modified release oral and transdermal dosage forms: Section I (pharmacokinetic and clinical evaluation)	Released for consultation in April 1998
CPMP/EWP/436/97	Clinical investigation of new vaccines	Released for consultation in July 1998
CPMP/EWP/1401/98 (in collaboration with QWP)	Investigation of bioavailability and bioequivalence	Released for consultation in December 1998

The Safety Working Party (SWP), chaired by Dr Per Sjöberg met twice in 1998. The working party gave special advice on pre-clinical and safety issues and was involved on a number of occasions in the preparation of scientific advice. In particular the working party addressed the need and extent of testing carcinogenic potential in relation to the ICH guideline (ICH topic S1A: need for carcinogenicity studies of pharmaceuticals, ICH topic S1B: testing for carcinogenicity of pharmaceuticals).

The SWP, in cooperation with the BWP, was involved in the preparation of the DNA vaccine and gene therapy related notes for guidance.

In conjunction with the SWP, an ad hoc group on new methods for testing the carcinogenic potential of medicinal products was held, chaired by Dr Per Sjöberg. This workshop confirmed the EU position held earlier, namely that there is insufficient information at present to predict or offer guidance on which of the new models may be most suitable for a particular medicinal product. The new models will be evaluated when more experience has been gained.

The following documents were adopted or released by the CPMP for consultation in 1998:

Reference number	Concept paper	Status
CPMP/SWP/160/98	Immunotoxicity and the need to update the notes for guidance on repeat dose toxicity and on non-clinical local tolerance testing of medicinal products	Adopted in February 1998

Reference number	Guidelines	Status
CPMP/SWP/997/96	Pre-clinical evaluation of anticancer medicinal products	Adopted in July 1998
CPMP/ICH/300/95 (S4)	Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)	Adopted in November 1998
CPMP/SWP/112/98	Safety studies for gene therapy products. This is an annex to the Note for guidance on gene therapy product quality aspects in the production of vectors and genetically modified somatic cells	Released for consultation in January 1998

Ad hoc CPMP groups

In addition to the CPMP working parties a number of ad hoc working groups met in 1998.

Ad hoc expert group on oral contraceptives

Chaired by Prof. Bo Odling, the group met once in 1998 to look at the cardiovascular risks associated with the use of these medicinal products.

Ad hoc working group on blood products

The group was created by the CPMP in April 1998 to address efficacy of safety aspects of blood products. The group's mandate (CPMP/1489/98) and work plan (CPMP/BPWG/1488/98) were adopted by the CPMP in July 1998. Dr Manfred Haase chairs the group.

Ad hoc expert group meeting on update of guidance on summary of product characteristics

Coordinated by Dr Mary Teeling, this group met three times in 1998 to propose new wording for most sections of summary of product characteristics. The group worked together with experts from each of the CPMP working parties, the EMEA ad hoc group on herbal medicinal products and also members of the quality review of documents group.

2.5. Ad hoc EMEA working group on herbal medicinal products

The ad hoc EMEA working group on herbal medicinal products met twice in 1998, chaired by Dr Konstantin Keller. In addition to members nominated by the Member States, the European Parliament representatives to the Management Board, the European Commission and observers from the European Pharmacopoeia also participate in the group.

Created in 1997, at the request of the European Commission, the group operates to prevent arbitration arising from the mutual recognition procedure for these medicinal products.

During its July 1998 meeting the group continued its discussion on the global assessment of scientific monographs and on the definition of criteria to assess the quality, safety and efficacy of herbal medicinal products. In December 1998, the group reported on its activities to the Management Board and to the European Commission.

The activities of the ad hoc group resulted in the following proposals:

Reference number	Title	Status
EMEA/adhocHMPWG/-33279/98	Proposal for new guidance 'Fixed combinations of herbal medicinal products with long-term marketing experience' - Guidance to facilitate mutual recognition and use on bibliographic data	Released for consultation in September 1998
	Comments and proposals for revision of the Notice to applicants Volume 2B Parts IC1 and II, including proposal for tabular formats specific to herbal medicinal products	Released for consultation in September 1998
EMEA/adhocHMPWG/-114/98	Good manufacturing practice: Comments and proposals for revision	Finalised in September 1998
	Proposals for revision of Note for guidance 'Quality of herbal remedies'	Finalised in September 1998
	Proposal for new guidance: 'Non-clinical testing of herbal drug preparations with long-term marketing experience' Guidance to facilitate mutual recognition and use of bibliographic data	Finalised in September 1998
	Notice to applicants Volume 2A and Volume 2B Parts IB1, IC2 and III - Comments and proposals for revision	Finalised in September 1998
	Comments on Part 4 of Annex to Council Directive 75/318/EEC of 20 May 1975 'Clinical documentation'	Finalised in September 1998
	Proposal for a core-SPC for <i>Valerianae radix</i>	Finalised in September 1998

2.6. Mutual recognition of medicinal products for human use



The mutual recognition or decentralised procedure is the second European Community licensing system that is being established in Europe with co-operation between the Member States.

The mutual recognition procedure has made considerable progress during 1998. The use of the procedure in 1998 was:

Mutual recognition procedure	Total submitted in 1998	Under evaluation in 1998	Ended positively in 1998	Arbitrations in 1998
New applications	183	30	179	1
Type I variations	482	152	327	-
Type II variations	344	147	204	4

Figures at 18 December 1998

The number of applications both submitted and completed has risen during 1998, compared with 10 procedures completed in 1995, 84 in 1996 and 147 in 1997. The very low level of arbitrations is another encouraging feature.

The Mutual Recognition Facilitation Group (MRFG) continues to meet at the EMEA every month on Monday of the CPMP week. The MRFG met under the chairmanship of Dr David Jefferys of the United Kingdom from January to June 1998 and Dr Christa Wirthumer-Hoche of Austria from July to December 1998. The MRFG and the Member States were particularly grateful for the support of the EMEA in providing meeting rooms for the Group and for the break-out sessions. The EMEA also provided the Secretariat to support the MRFG. The participation of the Commission during the MRFG meetings was very valuable. Observers from Iceland and Norway attended the MRFG from January 1998 in order to prepare for their full participation in the mutual recognition system from early in 1999.

During 1998, the MRFG concentrated upon improving the performance of the procedure. In order to avoid delays an automatic validation procedure for new application was introduced from 1 May 1998 for a six-month trial period. The great success of the trial meant that this was continued as an established part of the procedure from November and at the same time an automatic validation procedure was introduced to cover all type II variations.

The group undertook a major review of the operation of break-out sessions and the clarification phase. This was discussed in depth at an informal meeting of the MRFG organised in May during the UK Presidency. Following this, the Best Practice Guide was modified in July 1998 so that the deadline for comments from concerned Member States has been changed from day 60 to day 55 in order to increase the time for the clarification phase. Other changes were made to the break-out protocol document and a series of initiatives were put into place by the Member States to improve this part of the procedure.

In 1998 a total of 64 break-out sessions were organised by reference Member States and held at the EMEA. The MRFG reviewed the protocol for the handling of break-out sessions in order to improve the outcome of these meetings for clarification of serious public health concerns. It is important to mention that in 1998 there was a decrease of 48 % in the number of break-out sessions for new applications compared to the period 1995 to 1997.

The frequency of withdrawals of applications from individual Member States during the mutual recognition procedure is still an issue of concern, but also this number of partial withdrawals decreased in 1998 by about 40 % compared to the number during the transition period.

Version 3 of the tracking system, 'EudraTrack', for monitoring of the mutual recognition procedure became fully operational on 1 November 1998.

During the year an increasing number of Member States acted as reference Member State and nearly all Member States have now undertaken this important role. The number of finalised procedures by type is given in the table:

Total number of finalised procedures by type in 1998*		
	Number	Percentage
New active substances	35	19.6
Generics	45	25.1
Line extensions	26	14.5
Fixed combinations	22	12.3
OTC	5	2.8
Herbal	1	0.6
Others	45	25.1

* The number includes a total of 179 multiple procedures.

In order to classify the products in a more detailed way two additional categories were identified, namely for blood products and vaccines since November 1998. It is encouraging to see the wide range of applications now using the mutual recognition procedure.

In 1998 there was for the first time the annual update of mutually recognised licenses of influenza vaccines via the fast track procedure. Based on the first experience this procedure proved to be very successful. It worked well taken into account the adherence to the agreed timetable in general, the final approval dates and the positive outcome of all requested annual updates.

A major emphasis during the year was to increase the visibility of the mutual recognition procedure. The press release instituted in July 1997 has become a regular feature with increased statistical information and increased feedback. This is now published on the MRFG Internet site (<http://heads.medagencies.org>). Additional statistical information and standard operating procedure are also published on the website along with a list of contact points. It is intended that a product index of mutual recognition

procedures will be made available on the site early in 1999 and will be followed slightly later by the publication of summary of product characteristics of products which have been through mutual recognition.

A major workshop on transparency in the mutual recognition procedure was hosted by the UK in September 1998. Proposals are currently under discussion to increase transparency in the mutual recognition system and the possible development of mutual recognition public assessment reports.

Following the release of the 'Commission communication on the Community marketing authorisation procedures for medicinal products' (OJ C 229, 22.7.1998, p. 4) the Group had in-depth discussions on the document in order to clarify the situation and created several standard operating procedures, which are available on the MRFG website for information.

Significant issues remain to be addressed in the mutual recognition procedure but good progress was achieved during 1998. The close cooperation between all the stakeholders in the system provides an encouraging platform for the rapid expansion in the number of procedures, which can be expected over the next years.

3. MEDICINAL PRODUCTS FOR VETERINARY USE

3.1. Unit for the Evaluation of Medicinal Products for Veterinary Use

The Unit had a busy year working to fulfil its two major functions: the establishment of maximum residue limits (MRLs) for substances used in medicines for food-producing animals, and progressing centralised applications for new veterinary medicinal products. The structure of the Unit remained stable with Dr Peter Jones as Head of Unit and the Heads of Sector, Dr Jill Ashley-Smith and Dr Kornelia Grein.

Working towards the deadline of 1 January 2000 to set MRLs for all substances on the market before 1 January 1992 (so-called 'old substances'), the Safety of Residues Working Party, supported by the sector concerned headed by Kornelia Grein and her staff, has met the goals for setting MRLs for old substances in 1998. There however remains a considerable amount of work to complete before the deadline.

Significant efforts have been made in meeting the target of increasing industry's confidence in the centralised system in the veterinary sector. The efforts of Jill Ashley-Smith and her staff have seen a very significant increase in the number of centralised applications exceeding that forecast in the work programme for 1998-99.

The increasing awareness of the problems associated with antimicrobial resistance in human medicine is well recognised by the CVMP. Its working group of experts continues to make progress in evaluating the potential risks associated with the use of these products in veterinary medicine – a report is expected to be available by the middle of 1999. In addition the growing concerns about the lack of available medicines for particular indications in certain species, especially minor species, has necessitated the creation of an ad hoc group of committee members to look at new ideas for addressing the problem.

Within the VICH initiative, the Unit in its role of European Coordinator has continued to participate actively in progressing the harmonisation of testing requirements for registration of veterinary medicines amongst the major parties: EU, Japan and USA.

3.1. Unit for the Evaluation of Medicinal Products for Veterinary Use

3.2. Operation of the CVMP

3.3. Establishment of maximum residue limits

3.4. CVMP working parties

3.5. Mutual recognition of veterinary medicinal products



Reinhard Kroker



Cyril O'Sullivan

3.2. Operation of the CVMP

The CVMP began a second three-year mandate in January 1998. Five new members were nominated to the Committee. Details of membership are given in Annex 3. Professor Reinhard Kroker was re-elected chairman of the CVMP and Mr Cyril O'Sullivan was re-elected vice-chairman for the period 1998 to 2000.

Authorisations under the centralised procedure

A significant development in 1998 has been the change to Part B of the Annex to Council Regulation (EEC) No 2309/93 allowing applications to be lodged under the centralised system for new molecules intended to be used for companion (i.e. non-food-producing) animals as well as for food-producing animals. As forecast in the 1998-99 work programme this positive step has already contributed to an increase in the number of centralised applications in the veterinary sector.

Industry showed its confidence in the centralised system in 1998 with an increase in the number of applications submitted to the Agency. A total of 14 applications were made, a 55 % rise over the number forecast for this year. It is also worth noting that many of the applications are from companies who have already selected the centralised route for a previous submission and are expressing their satisfaction with the role played by the EMEA and CVMP.

Applications are almost equally divided between mandatory biotechnology applications and optional applications for innovative medicines where the applicant had a choice of procedure under Part B of the Annex to Council Regulation (EEC) No 2309/93.

The four opinions adopted by the CVMP in 1998 as well as those 14 applications currently under evaluation, have all been processed within the time-frame, and with no increase in recruitment of scientific and administrative staff assigned to the sector responsible. Details of Community marketing authorisations granted for veterinary medicinal products are given in Annex 7.

Interested parties from a wide sphere continue to attend quarterly briefing meetings with members of CVMP regularly and also the regular Info-days held jointly with industry.

With the increasing support work necessitated by the entry into the market of a growing number of centrally approved products, post-marketing activities including processing of variations (according to numbers forecast) and effective pharmaco-vigilance monitoring are being handled effectively.

An important workshop was held on pre-submission activities with potential applicants. The meeting was well attended and allowed a useful exchange of information on the critically important issues to be addressed in the pre-submission phase in the four months leading up to the submission of a dossier. The necessity to address such pre-submission issues ensures a far more streamlined approach to the evaluation phase of the procedure.

The Committee continued to reflect on those areas of regulating veterinary medicines where further advice and guidance appears necessary for applicants on certain procedural aspects and the testing of medicinal products themselves.

Two further guidelines on the establishment of maximum residue limits were adopted, one on setting MRLs in *salmonidae* and other fin fish and one addressing the issue of pharmacological activity of excipients contained in veterinary medicinal products. Several guidelines have also been released for consultation on testing immunological veterinary medicines, pharmacovigilance reporting, setting withdrawal periods in milk and quality issues.

Reference number	Title of guideline	Status
EMA/CVMP/153b/97	Establishment of MRLs for <i>salmonidae</i> and other fin fish	Adopted in January 1998
EMA/CVMP/004/98	Excipients in the registration dossier of a veterinary medicinal product	Released for consultation in January 1998
CVMP/IWP/043/97	Use of adjuvanted veterinary vaccines	Released for consultation in February 1998
EMA/CVMP/112/98	Harmonisation of requirements for equine influenza vaccines specific requirements for substitution or addition of a strain	Released for consultation in March 1998
EMA/CVMP/141/98	Revised rapid alert system (RAS) in veterinary pharmacovigilance	Released for consultation in June 1998
EMA/CVMP/345/98	Guideline for competent authorities for the verification and evaluation of pharmacovigilance information for veterinary medicinal products	Released for consultation in July 1998
EMA/CVMP/315/98	Development pharmaceuticals for veterinary medicinal products	Released for consultation in August 1998
EMA/CVMP/473/98	Determination of withdrawal periods for milk	Released for consultation in December 1998

The CVMP prepared comments on the draft Codex Alimentarius guideline on residues at injection site, which served as the basis for the European Union's position on this issue at the meeting the Codex Committee on Residues of Veterinary Drugs in Food in September 1998. However, as the Codex Committee has not yet reached a conclusion, the revision of the CVMP guideline on injection site residues was deferred.

The EMA continues to play an important role in coordinating the EU regulatory input into VICH where progress on the drafting of guidelines has been very encouraging. Two quality guidelines on analytical validation have now been finalised and will be implemented in the EU, Japan and USA in October 1999. In addition draft guidelines on further quality aspects including stability testing and control of impurities, as well as anthelmintic efficacy testing, environmental impact analysis, and good clinical practice have been submitted to the Steering Committee and released for consultation. Preparatory work on a second series

of topics, including testing of biologicals, and pharmacovigilance is now well under way. The first public conference for VICH is scheduled for November 1999 in Brussels.

Availability of medicines

The CVMP paid increasing attention in 1998 to what is becoming one of the major issues for animal health and welfare in Europe; the decrease in availability of veterinary medicines. Much of the problem relates to the inadequacy of data being provided to defend many old substances for which the CVMP is endeavouring to establish maximum residue limits. The net result may be a loss of important medicines from the EU market after the deadline for setting MRLs for those substances by 1 January 2000. In addition there is concern at the few products being licensed for minor species.

The Committee has established a working group of experts, chaired by Professor Christian Friis, to examine ways of addressing the issue. The CVMP has reported on its deliberations to the Management Board of the Agency who held a brainstorming session on the matter at its June 1998 meeting. Concrete proposals are now being considered based on efforts to identify precisely the indications and species for which products will cease to be available. A collaborative effort is in progress with European Commission Directorate-General for Industry to assist in resolving the problem.

3.3. Establishment of maximum residue limits (MRLs)

Annexes to Council Regulation (EEC) No 2377/90	Old substances	New substances
Annex I: <i>Substances for which an MRL has been established</i>	52	15
Annex II: <i>Substances for which it is not necessary to establish an MRL</i>	339	11
Annex III: <i>Substances for which a provisional MRL has been established</i>	42	15
Annex IV: <i>Substances for which no MRL can be established</i>	11	0

Maximum residue limits for new substances

The number of MRL application under Article 6 of Council Regulation (EEC) No 2377/90 received by the EMEA in 1998 remained relatively stable and came close to the forecasted numbers. A total of 14 applications were received, including four full applications and 10 applications for extensions to other species or modification to existing MRLs.

The target to complete all validations within 14 days was fully met, the average number of days being 11, considerably less than the 30 allowed for in the legislation. In 1998 the CVMP adopted opinions for 25 substances recommending their inclusion in Annex I, II or III. In the case of two new applications and one modification, no recommendation for inclusion in Annex I, II or III was possible, because of the inadequacy of the data provided. For a further five substances the assessment could not be concluded and the applicants were requested to provide additional data.

During the year the CVMP undertook all assessments within the time frame laid down by Council Regulation (EEC) No 2377/90. The initial evaluation resulting in an opinion or a list of questions took on average 114 days of the 120 days provided for, while the assessment of the responses to lists of questions was completed in all cases within the 90 days provided by said Council Regulation.

Details of new substances for which MRLs have been established are given in Annex 7.

Maximum residue limits for old substances

The Committee completed the first evaluation for all defended old active principles by March 1998. Work throughout the rest of 1998 concentrated on the assessment of responses provided by companies to requests for additional data in the lists of questions.

In order to fulfil the Committee's obligations under Council Regulation (EC) No 434/97 (OJ L 67, 7.3.1997, p.1) to conclude first assessment of all defended old substances by 1 January 2000, a work plan was agreed by the Safety of Residues Working Party. Factors to be considered included:

- *last deadline for submission of proposals to CVMP (June 1999);*
- *date foreseen for submission of the responses;*
- *workload of the rapporteurs;*
- *realistic number of substances which can be assessed during each meeting;*
- *similarity of substances.*

In September 1998, with the full agreement of industry, the CVMP agreed to make this plan publicly available. This demonstrates the Committee's commitment to work within the legal timeframe, whilst at the same time recognising the importance of transparency in this matter in the light of ongoing discussion in the animal health sector on the availability of medicines.

The CVMP made significant progress on the assessment of herbal remedies and substances used in homeopathic veterinary medicinal products and made recommendations for 31 herbal remedies. The data provided concerning all defended substances intended to be used in homeopathic veterinary medicinal products were reviewed.

The preparation of a document on risk assessment was deferred until the first quarter 1999 due to a re-prioritisation of objectives where highest priority was given to the timely processing of MRL applications for old and new substances.

3.4. CVMP working parties

A full series of the CVMP working party meetings had been planned for 1998 but meetings had to be cancelled or deferred until early 1999 because of the financial contingency plan necessitated by cuts to the Agency's budget. Nevertheless a significant amount was achieved by all the working parties concerned.

Safety of Residues Working Party

The Safety of Residues Working Party, chaired by Mr Gabriel Beechinor, held seven meetings each of three days in 1998. At the beginning of 1998 recommendations for inclusion of 311 substances in Annex I, II, III or IV of Council Regulation (EEC) No 2377/90 had been made with the total number of substances still to be assessed standing at approximately 200 (with the exception of herbal remedies and substances used in homeopathic veterinary medicinal products). The commitments previously given in the 1998 EMEA Work Programme, to complete the assessment of MRL applications for at least 100 substances have been completed satisfactorily and even exceeded (114).

The CVMP was unable to establish MRLs for nine old substances because of the inadequacy of data supplied by the applicant concerned and applications for 21 substances have been withdrawn. This situation has raised concerns because MRLs cannot be set of an increasing number of substances which will have an impact on the problem of availability of veterinary medicines; a subject which is being addressed in some consideration by the CVMP.

The working party submitted for the consideration of the CVMP a guideline for the establishment of withdrawal periods for milk which was adopted by the CVMP and released for consultation in December. At the request of the CVMP, the working party also initiated the preparation of a guideline for the assessment of the effect of antibiotics in dairy starter cultures.

In addition, the CVMP prepared a scientific position for discussion at the Codex Alimentarius meeting in Washington on a number of important issues relating to consumer safety.

Efficacy Working Party

The Efficacy Working Party (EWP) met three times in 1998, chaired by Dr Lisa Kaartinen. Significant progress was made on the review of the guideline for conduct of pharmacokinetic studies in animals. The intramammary guidelines have also been reviewed and incorporated into a single guideline, which is currently being revised. Now that the VICH working party on anthelmintic efficacy has prepared a draft guideline, this will facilitate review of the existing anthelmintic guidelines. The CVMP agreed to a mandate for the EWP to develop a new guideline for non-steroidal anti-inflammatory drugs in view of the difficulties resulting from the absence of such a guideline.

Immunologicals Working Party

The Immunologicals Working Party (IWP) met three times in 1998, with Professor Paul-Pierre Pastoret as chairman.

The following notes for guidance or position papers were prepared by the IWP and following consultation adopted by the CVMP:

Reference number	Title of guideline	Status
CVMP/IWP/029/97	Definition of a new biological active substance in terms of active, passive immunity and immunomodulators which then constitute a new active ingredient	Adopted in February 1998
CVMP/IWP/038/97	Batch potency testing of immunological veterinary medicinal products	Adopted in September 1998
CVMP/IWP/042/97	Indications and specific claims for veterinary vaccines	Adopted in September 1998
CVMP/IWP/007/98	DNA vaccines non-amplifiable in eukaryotic cells for veterinary use	Released for consultation in November 1998

Pharmacovigilance Working Party

Chaired by Professor Agostino Macri, the Pharmacovigilance Working Party met twice in 1998. Although the number of centrally approved products being approved is significantly increasing, very few adverse reactions are being reported, so that the working party has focussed mainly on periodic safety updates for monitoring safety of centrally approved products.

At the request of the CVMP progress has been made in drafting a number of guidelines notably one on post-marketing surveillance, to which industry was invited to contribute early in the development process. The Veterinary Dictionary of Defined Terms (Veddra) is now complete and incorporated in the EudraWatch system for communication of adverse reports between Member States, Commission and EMEA.

The working party has continued to monitor serious reports relating to a few nationally approved products and made recommendations for precaution statements on product labelling, which the respective countries have implemented.

Joint CPMP/CVMP Quality Working Party

Work commenced on the draft guidelines on development pharmaceuticals for veterinary products and the annex to the in-use stability guideline concerning the shelf life of sterile veterinary medicinal products. A position paper on premixes for medicated feeding stuffs for veterinary use versus powders/granules for oral use or use in drinking water was drafted and finalised following a period of consultation. Details of these can be found in Chapter 4.

During 1998 the working party continued to follow the developments of the VICH initiatives and provided comments on draft guidelines including those on the stability of new active substances, new products and premixes. The working party also nominated an expert on moisture and formaldehyde in response to the call by the VICH Steering Committee for assistance following the addition of further priority topics. A rapporteur was also appointed to consider the annex to the VICH stability guideline for storage conditions for veterinary medicinal products.

Ad hoc working group on antimicrobial resistance

In order to support the work of this group a national expert on secondment from Germany was appointed to the secretariat staff for a period of nine months.

A major task has been to collate and interpret an enormous amount of data collected by experts in their respective countries on antimicrobial resistance. Data have been summarised on use patterns of antimicrobials in the Community, routes of administration as well as an estimate of amounts of products used in veterinary medicine in the Community.

Because of the enormous amount of data available, the interpretation of resistance patterns have initially been confined to *Salmonella* and *E. Coli* with a view to further examination of other bacteria in the next phase.

A hearing with industry was arranged in September where a very useful exchange of information took place as well as ideas on optimising progress in the months ahead. A report on risk assessment is planned for the second half of 1999.

3.5. Mutual recognition of veterinary medicinal products

The Veterinary Mutual Recognition Facilitation Group (VMRFG) has continued to meet each month at the EMEA, providing a forum for the Member States to discuss applications under the mutual recognition procedure, together with other organisational and procedural matters. The group has been chaired by the United Kingdom since its inception at the request of the various presidencies.

During 1998 there were 22 new applications finalised with four in progress. A total of seven type I and five type II variations were finalised and 20 type I and 12 type II were in progress at the end of 1998.

During 1998 the number of mutual recognition applications continued to rise steadily. Now that the transitional arrangements have ended and it is no longer possible to apply separately for national marketing authorisations in several Member States, the number of mutual recognition applications is expected to increase.

During the year there were two meetings between representatives of the group and Fedesa and, as a result of these meetings, the decision reports relating to organisational issues were released to industry. Several other documents were also approved for release to industry and for public information and work is going forward on an Internet website for the VMRFG so that documents may be made more easily available.

4. TECHNICAL COORDINATION UNIT

Building on foundations laid in 1997, the Unit workload increased some 20 % during 1998 with 44 members of staff, an increase of one new post. The structure of the Unit remained stable under Karel de Neef, Head of Unit, and his four Heads of Sector, Stephen Fairchild, Beatrice Fayl, Sylvie Bénéfice and Michael Zouridakis. David Drakeford was appointed Deputy Head of IT Sector.

Commitment to continuous improvement has taken place through goal-oriented management, increased training and active support to the quality management system programme. During the year, systematic time recording was introduced and this was used as a basis for improved planning. By analysing the various activities within the Unit, resources were better allocated and monitored on a monthly basis against expected results.

The Unit coordinated the Agency's quality management initiative and a quality manager, Marijke Korteweg, was appointed to continue and maintain the progress of the initiative. At the end of 1998 a programme to recruit internal auditors in preparation for the planned implementation of internal audit procedures in early 1999 was undertaken. Internal auditing will help to achieve continuous improvement of the 'quality manual' and the systems and processes at the EMEA.

The principal effect of the contingency plan, implemented for the second half of 1998 to reduce expenditure in line with income, was a freeze on recruitment resulting in eight posts planned for the year not being filled. Meetings of the ad hoc Inspectors Groups planned for the last quarter of 1998 were postponed and the start of work on new procedures delayed. The IT sector postponed planned expenditure relating to remote access and equipment for new staff.

An improved version of the application tracking system (ATS) was introduced in 1998 with a number of new features, including the handling of variations, maximum residue limits, inspections and certification of medicinal products.

4.1. Coordination of inspections and quality of human and veterinary medicines

4.2. Document management and publishing

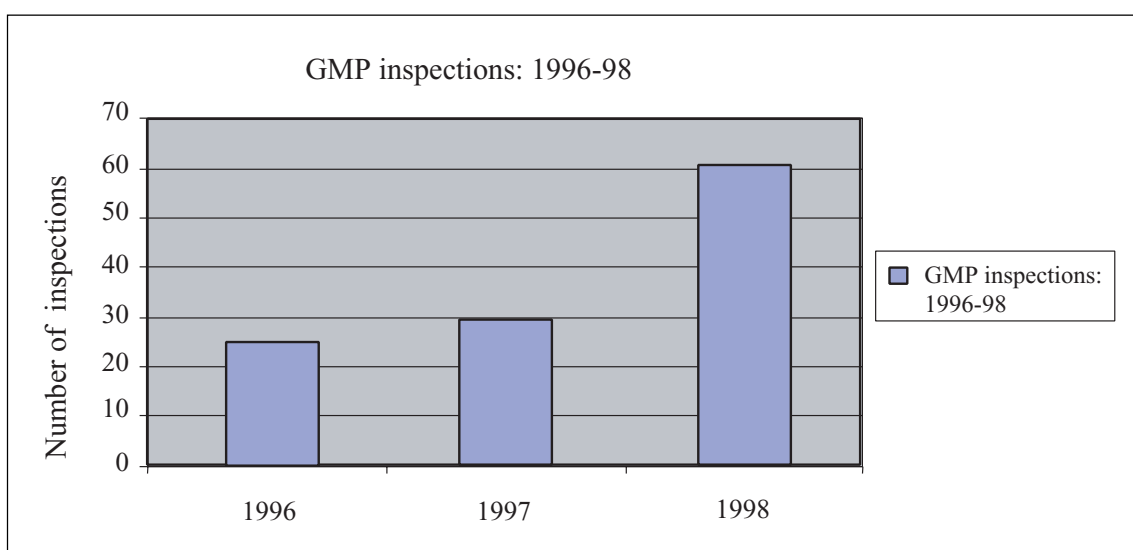
4.3. Conference services

4.4. Information technology

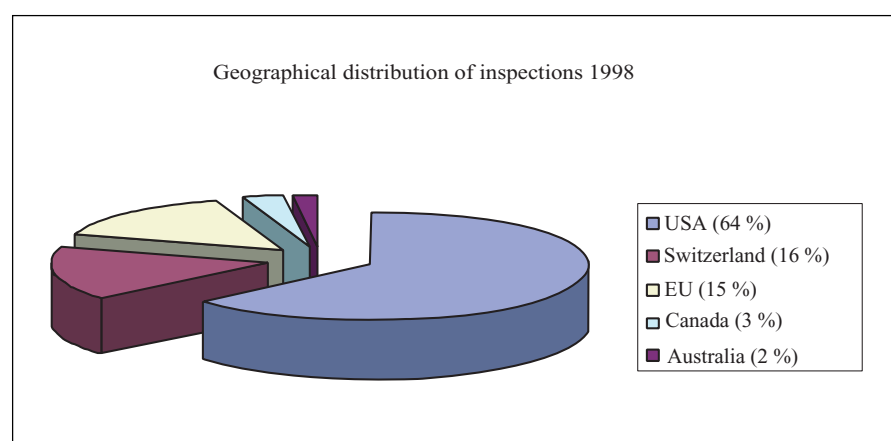
4.1. Coordination of inspections and quality of human and veterinary medicines

Good manufacturing practice (GMP) and good clinical practice (GCP) inspections

The process for the organisation and coordination of pre-authorisation inspections for applications under the centralised procedure has been consolidated and is now a routine task. A total of 61 inspections were carried out for 39 applications, representing inspections for 64 % of the total applications for 1998. Inspection teams were drawn from 11 of the 15 Member States with 62 % of the teams being provided by Belgium, Germany and United Kingdom.



Harmonisation in relation to Community GMP inspections was advanced by the work of the Agency's ad hoc GMP Inspectors Group. This included the implementation of standard format GMP inspection reports as well as a template for manufacturing authorisation reports.



During 1998, harmonised inspection procedures were developed at three ad hoc meetings attended by GCP inspection services from the EU Member States together with observers from EEA and Cadreac countries. These harmonised procedures are due to be implemented during 1999.

A trial to establish the basis for routine testing of centrally authorised products was carried out in 1998. This involved taking samples of nine centrally authorised products from the supply chain/market place and submitting them to the Official Medicines Control Laboratories of the EU Member States. This work was carried out in collaboration with the Rapporteurs and Co-Rapporteurs for the products involved and the European Department for the Quality of Medicines. Results indicated that the quality of the products tested is satisfactory and the trial provided useful experience. On the basis of this trial, recommendations for a routine testing system were prepared for submission to the CPMP/CVMP and the European Commission.

The European Department for the Quality of Medicines

Part of the Council of Europe and based in Strasbourg, the European Department for the Quality of Medicines is staffed by about 100 persons. The Department is divided into four divisions: scientific secretariat of the European Pharmacopoeia; physico-chemistry, immunology, microbiology and cell culture laboratories; the European network of official medicines control laboratories and biological standardisation; and print and electronic publications and databases.

European Pharmacopoeia: *regular and continuing exchanges*

The European Pharmacopoeia is very much part of the European regulatory framework. EMEA participates in the work of the European Pharmacopoeia Commission as part of the EU delegation. The Pharmacopoeia secretariat and experts similarly participate in meetings of the European Commission Pharmaceutical Committee and also in a number of EMEA working groups. These exchanges make it possible to meet licensing needs and adapt the European Pharmacopoeia according to requests made by the various EMEA working parties.

The European Pharmacopoeia also maintains an up-to-date list of standard terms used in product information for health professionals and patients. This list is available in 15 languages, including all 11 official EU languages.

European Network of Official Medicines Control Laboratories: *coordinated implementation and development*

Set up in 1994 as a joint project between the EU and Council of Europe, the network allows the co-ordination of a number of activities in EU and EEA-EFTA States. These include batch release procedures, sampling of products and market surveillance. The EMEA participates in all meetings of the network and is a member of the internal advisory group. Future developments of the network will be coordinated with the EMEA in particular to take into account quality control needs of the European authorisation system.

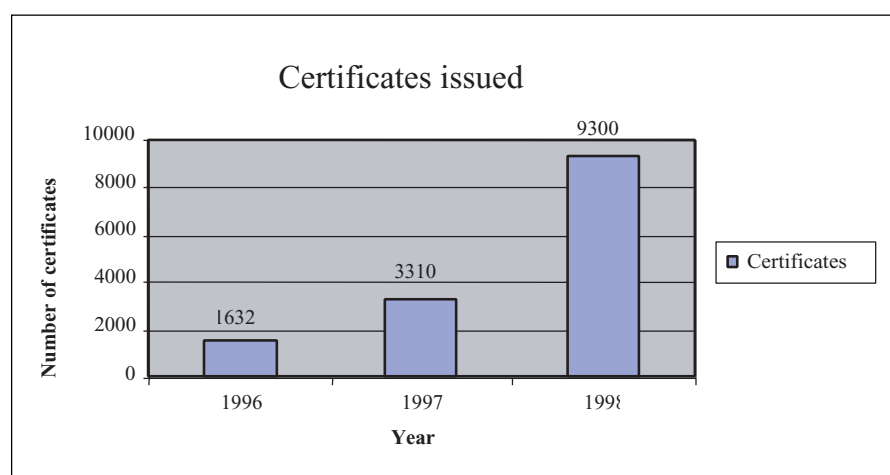
Crisis management

The sector was able to develop its capability and procedures for handling product quality-related problems based on the experience of three specific incidents during the year. In all cases the problems were resolved without risk to public health or adverse impact on the availability of the product involved.

Mutual recognition agreements (MRAs)

A significant amount of preparatory work has been carried out for the pharmaceutical annex of the MRA with Canada that was signed off during the year. The major part of this work has been in preparing for the equivalence assessment process and the management of the confidence building and operational phases of the Agreement. Preparations also started for the implementation of the Agreement with the USA and the exchange of information under the Agreements with Australia and New Zealand.

Certification of medicinal products



The major part of the increase in demand for certificates came from a few large requests in the middle of the year, which caused some temporary delays in deliveries. October saw two major improvements in the system with the launch of optional simplification of the scope of certification (which will reduce the numbers of certificates issued) and introduction of a procedure for the legalisation of EMEA certificates by the European Commission's Representation in the UK. The Agency also strengthened its links with user companies and receiving countries through a series of liaison meetings and workshops.

Joint CPMP/CVMP Quality Working Party

The working party, chaired by Dr Jean-Louis Robert, met on three occasions, two of which were with a full complement of veterinary experts. The working party provided support for the EU position on a number of ICH quality topics and also continued the development of a number of EU quality guidelines.

Reference number	Title	Status
CPMP/QWP/155/96	Note for guidance on development pharmaceuticals	Adopted in January 1998
CPMP/QWP/159/96	Note for guidance on maximum shelf-life for sterile products for human use after first opening or following reconstitution	Adopted in January 1998
CPMP/QWP/297/97	Note for guidance on summary of requirements for active substances in part II of the dossier	Adopted in January 1998
CPMP/QWP/609/96	Note for guidance on the declaration of storage conditions for medicinal products in the products particulars	Adopted in January 1998
CPMP/QWP/556/96	Note for guidance on stability testing of existing active substances and related finished products	Adopted in April 1998
CPMP/QWP/576/96	Note for guidance on stability testing for a type II variation to a marketing authorisation	Adopted in April 1998
CPMP/QWP/158/96	Note for guidance on dry powder inhalers	Adopted in June 1998
CPMP/QWP/054/98	Decision trees for the selection of sterilisation methods	Released for consultation in January 1998
CPMP/QWP/604/96	Note for guidance on modified release oral and transdermal dosage forms: section II (quality)	Released for consultation in April 1998

4.2. Document management and publishing

The working procedures of the working group on the quality review of documents (QRD) were changed in 1998. By introducing an electronic procedure via EudraNet for the review of product information, the monthly meetings of the group were replaced by bi-monthly meetings from September onwards.

QRD work was carried out in respect of 52 applications. The product information templates for human and veterinary products were updated, and a number of reference documents providing detailed guidance on terminology and style finalised. All these documents were published on the EMEA Internet site, together with links to relevant legislation and other supporting documentation.

In order to provide support to the QRD, an internal product information quality (PIQ) team composed of project managers was created to review product information texts in all EU official languages. A second team, the secretarial PIQ team, was set up to perform preliminary formal checks on the documents. The QMS improvement team charged with linguistic and information quality issues produced a time-line and drafted a standard operating procedure.

As a consequence of the standardisation work the volume of translated pages was able to be optimised, with some 4 200 pages in total being translated in 1998. The Luxembourg Translation Centre is now fully staffed and this, together with clear and open communication between the EMEA and the Translation

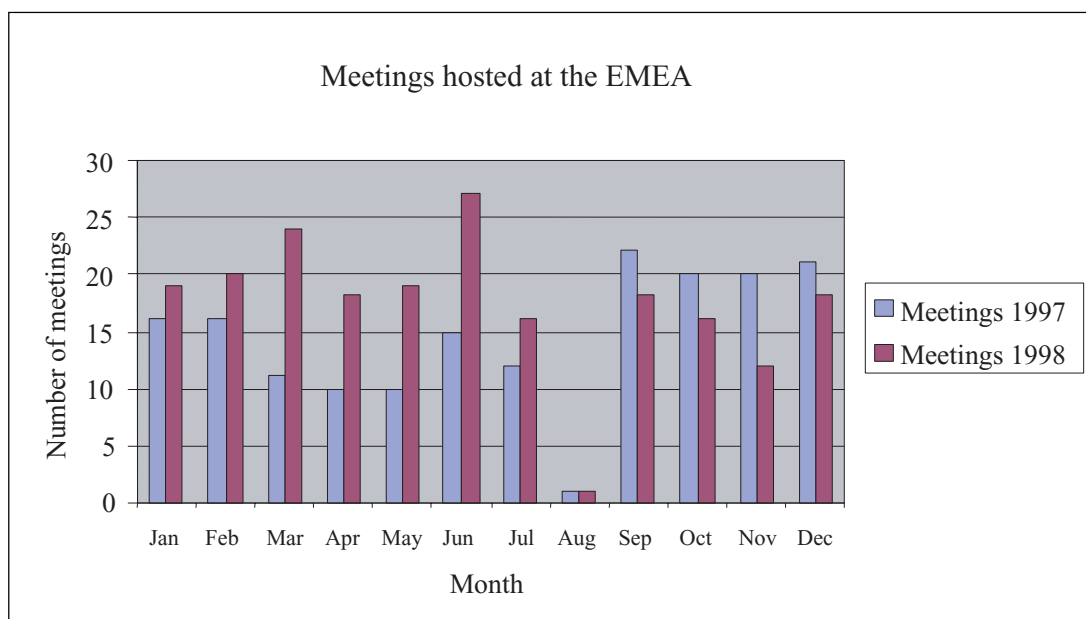
Centre, has contributed to a significant improvement in the quality and timeliness of the translations delivered by the Centre.

The number of subscribers to the EMEA subscription service increased to 221 at the end of 1998. An updated and improved version of the CD-ROM was issued to all subscribers during the first half of the year. The number of requests for documentation received by the document management and publications sector doubled in 1998 with the over 2 200 received.

4.3. Conference services

Meetings and delegates

During the first half of 1998, the number of meetings held at the EMEA as compared to 1997 increased by 55 %, to 121. The implementation of the contingency plan over the second half of 1998 resulted in the number of meetings hosted for the year totalling 208. Staff numbers remained unchanged during the year.



Together with an experienced pool of external conference support staff, the sector provided all necessary services to delegates participating in meetings at the EMEA. Almost 90 % of delegates elected to use the EMEA travel and accommodation services to make bookings throughout the year. A questionnaire concerning services offered by the sector was circulated in April 1998 to all delegates and comments acted upon.

A total of 2 170 delegate visits were reimbursed in 1998. The introduction of the new SI2 financial system in July allowed separate reimbursements of individual transactions for delegates, hotels, travel agents and national authorities. For the majority of transactions, this has considerably reduced the time required for the reimbursement process, from four to two weeks.

Interpretation needs were re-examined and the languages provided tailored to the real needs and expectations of delegates. A total of 347 interpretation days were provided in 1998. A number of meetings were held with the European Commission Joint Conference and Interpretation Service to enhance the service provided for meetings at the EMEA and also concerning the standardisation of specialist terminology.

Reprographics

The workload of the reprographics service reflected both the cyclical activity pattern of the EMEA (about 23 000 copies per day on routine days and 115 000 copies per day during CPMP meetings) and increasing levels of activity. Overall, the number of photocopies, mainly in support of meetings, reached 7 405 000. This represents approximately three-quarters of the total photocopies made at the agency, of which two-thirds were for the CPMP.

Various improvements were made in 1998 including changes in the flow of documents and the installation of new higher capacity machines.

Video-conferencing

Video-conferencing was increasingly utilised for routine consultations with the European Commission and for small meetings with industry and other partners of the EMEA. It also proved to be a successful tool for securing external participation in large meetings taking place in the EMEA's main conference rooms.

A survey of the facilities of national competent authorities was carried out at the end of 1998 with a view to improving the use of video-conferencing both for core EMEA meetings and in support of the mutual recognition procedures.

4.4. Information technology

The IT sector provide computer services to EMEA staff and delegates. Activities are divided into support for daily operations of the agency and the design, testing and implementation of new facilities.

IT platform and user support

Increased compatibility with the Commission and the agency's EudraNet partners is being achieved as work on consolidation of the Windows NT platform continues. During 1998, the Oracle database engine was set up, a separate development and test environment was put in place and a number of specialised tools were made available to assist the users of the system. Improvements to the cabling infrastructure are being undertaken.

Appropriate training on IT tools was fully established in 1998 with a corresponding decrease in requests for assistance in the use of software.

Projects

SI2, the budget management system written specifically for the Commission, was successfully implemented during the year, automating a large part of the financial processing system. New features are being developed and added in response to the agency's requirements. ActiTrak, an activity and time-tracking system, was implemented throughout the agency and is being used to monitor key fee-related and non-fee related activities of the EMEA. Issues relating to the management of multiple languages are being addressed and work on programs dealing with these issues, including standardisation of terminology, is ongoing. Work on enhancing EudraWatch, the pharmacovigilance database, continued in 1998. The year 2000 problem is under review to ensure that full compliance is achieved.

European Technical Office for Medicinal Products (ETOMEP)



ETOMEP is part of the European Commission Joint Research Centre's Institute for Health and Consumer Protection. Based at the EMEA in London, the group supports the IT network that connects all national competent authorities, the European Commission and the EMEA itself.

All connections to the EudraNet (European Union drug regulatory authorities' network) were completed in 1998. The IDA programme, which is managed by DG III, funds the work of ETOMEP. Progress in the secure electronic exchange of documents was made in 1998 and a number of committees and working groups took advantage of this.

The EMEA website, managed by ETOMEP, was re-launched in 1998. The new design reflects the rapid growth of both the quantity and type of documents made available on the site. It also aims to respond to the agency's policy on transparency and public access to documents. ETOMEP also worked on the launch of the DG III regulatory *EudraLex* site (see Annex 8 for details).

In addition to work on the application tracking system (ATS), important results were achieved in 1998 in the development of the EudraTrack, a tracking system for the mutual recognition procedure. Version 3.0 was introduced in October 1998 permitting a fully computer-based system superseding the previous fax-based procedure and enhancing operational transparency. EudraTrack is managed by the national competent authorities and operated by ETOMEP.

5. ADMINISTRATION UNIT

5.1. Personnel and support services

5.2. Accounting

The unit structure remained stable under its Head of Unit Mr Marino Riva and the Heads of Sector, Ms Frances Nuttall and Mr Gerard O'Malley.

5.1. Personnel and support services

The EMEA does not have permanent officials, but is currently staffed by temporary agents recruited through open competitions. Recruitment follows the rules and practices of the EU institutions and successful candidates are offered five-year renewable contracts.

Due to budgetary restraints, there has been a modest increase in the number of staff serving at the EMEA in 1998.

EMEA staff	31.12.1996	31.12.1997	31.12.1998
A			
- temporary agents	45	70	73
- auxiliary staff	1	2	0
B	17	21	22
C and D	37	50	59
Total EMEA staff	100	143	154
National experts on secondment	3	2	3
External interim staff	10	9	9

While there are no formal national quotas, the Agency has sought to respect the balance of nationalities of the European Union. The staff comes from throughout the European Union.

Nationalities	B	DK	D	EL	E	F	IRL
A	6	2	8	3	4	11	6
B	5	1	2	2	1	1	0
C	4	3	5	3	3	7	2
D	0	0	0	0	1	0	0
Total temporary and auxiliary agents	15	6	15	8	9	19	8
National experts	0	1	1	0	0	0	0
Interims	0	1	0	1	1	1	0
TOTAL	15	8	16	9	10	20	8
Nationalities	I	NL	A	P	FIN	S	UK
A	6	3	2	2	2	2	16
B	3	1	0	0	0	0	6
C	3	2	0	1	4	1	17
D	0	0	0	1	0	0	2
Total temporary and auxiliary agents	12	6	2	4	6	3	41
National experts	1	0	0	0	0	0	0
Interims	1	2	0	1	0	1	0
TOTAL	14	8	2	5	6	4	41

The establishment plan adopted by the Management Board as part of the 1998 budget envisaged recruitment up to 184 members of staff. The delay in the reform of the fee regulation meant that only six new scientific administrators were recruited in 1998 and, for budgetary reasons, they could only start in November 1998. This delay in recruiting additional staff made for increased pressure on the staff as the work volume has continued to be intense.

A survey carried out as part of the quality management system clearly showed that staff across the agency are consistently working long hours. Additional personnel are needed and the recruitment delay can only be sustained for a limited period. Personnel practices, in particular in the area of performance evaluation and training, were examined and validated as part of the quality management initiative in 1998. A number of new recommendations, including those concerning the integration of new staff members, were implemented during the year.

The agency's commitment to training of its staff continued in 1998, with staff receiving on average four days of training. In addition to the established programmes, specific training courses were held on the nature of the managerial role and responsibilities, how to deal with cultural differences, and also media handling. The European Commission Secretariat-General and UK Representation Office also made presentations on the European Union to the Agency's staff.

5.2. Accounting

Analytical accounting

The EMEA continued its analytical costing exercise in 1998 and has cooperated with heads of national authorities in an attempt to achieve a better understanding of the costs of the European authorisation system.

As part of the agency's continuing efforts to have a better understanding of the costs of the centralised procedure, a time management system – ActiTrak – was introduced in 1998. Information from this will help identify time spent by staff on different activities and hence contribute to a better understanding of resource allocations for the fee and non-fee related activities of the EMEA. It is hoped that initial results will be available towards the end of 1999.

Budgetary accounting system

An integrated computerised system for budget and financial management, SI2, was introduced in May 1998. The system was initially developed and made available by the European Commission, although it has been adjusted to meet special requirements of the EMEA.

Budget and accounting data were transferred in mid-1998 and the system is now working well, and includes the production of reports for budget monitoring and other purposes. On the revenue side, plans to link the current fees database to the SI2 system were progressed in 1998.

Annexes

1. Membership of the Management Board
2. Membership of the Committee for Proprietary Medicinal Products
3. Membership of the Committee for Veterinary Medicinal Products
4. National competent authority partners
5. EMEA budgets for 1996 to 1998
6. CPMP opinions in 1998 on medicinal products for human use
7. CVMP opinions on medicinal products for veterinary use
8. Reference documents

Annex 1

MEMBERSHIP OF THE MANAGEMENT BOARD

Chairman

Strachan HEPPELL

European Parliament

Gianmartino BENZI

Dietrich HENSCHLER

Alternates

Dame Rosalinde HURLEY

Jean-Pierre REYNIER

European Commission

Stefano MICOSSI

Joaquim HEINE

Alternates

Jörn KECK ⁽¹⁾

Belgique/België

André PAUWELS ⁽²⁾

Michel CHOJNOWSKI

Danmark

Ib VALSBORG

Ib Bo LUMHOLTZ

Deutschland

Hermann Josef PABEL

Gerhard Josef KOTHMANN

Ελλάδα/Greece

Gerosimo KAVVADIAS

Nikolaos KOKOLIS

España

Federico PLAZA PIÑOL

Quintiliano PÉREZ BONILLA ⁽³⁾

France

Jean-René BRUNETIÈRE

Jacques BOISSEAU

Ireland

Tom MOONEY

John Albert COSTELLOE

Italia

Nello MARTINI ⁽⁴⁾

Romano MARABELLI (Vice-Chairman)

Luxembourg

Mariette BACKES-LIES

Nederland

André BROEKMANS

Christian VAN DER MEIJS

Österreich

Alexander JENTZSCH

Ernst LUSZCZAK

Portugal

José António ARANDA da SILVA

Maria Armanda MIRANDA

Suomi/Finland

Kimmo LEPPÖ

Hannes WAHLROOS

Sverige

Birgitta BRATTHALL

Anders BROSTRÖM

United Kingdom

Keith JONES

Michael RUTTER

⁽¹⁾ Jörn Keck replaced Guy CRAUSER as of the 30 September 1998 meeting.

⁽²⁾ André Pauwels replaced Jean-Pierre DEROUBAIX as of the 3 June 1998 meeting.

⁽³⁾ Quintiliano Pérez Bonilla replaced Valentin ALMANSA SAHAGÚN as of the 19 February 1998 meeting.

⁽⁴⁾ Nello Martini replaced Vittorio SILANO as of the 2 December 1998 meeting.

Annex 2

MEMBERSHIP OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Chairman

Prof. Jean-Michel ALEXANDRE

Belgique/België

Mr Geert DE GREEF
Dr Daniel BRASSEUR

Danmark

Dr Ib Bo LUMHOLTZ ⁽¹⁾
Dr Gorm B. JENSEN

Deutschland

Prof. Alfred HILDEBRANDT
Dr Manfred HAASE ⁽²⁾

Ελλάδα/Greece

Mr Michalis AVGERINOS ⁽³⁾
Mrs Julia YOTAKI

España

Mr José Félix OLLALA MARAÑÓN
Prof. Fernando de ANDRES-TRELLES

France

Dr Eric ABADIE
Prof. Jean-Hughes TROUVIN

Ireland

Dr Mary TEELING (Vice-Chairman)
Dr David LYONS

Italia

Prof. Giuseppe VICARI
Prof. Silvio GARATTINI

Luxembourg

Dr Jean-Louis ROBERT
Ms Jacqueline GENOUX-HAMES

Nederland

Dr Hans van BRONSWIJK
Mr Willem van der GIESEN

Österreich

Prof. Hans WINKLER
Dr Christa WIRTHUMER-HOCHE

Portugal

Prof. Rogério GASPAR ⁽⁴⁾
Prof. Cristina SAMPAIO ⁽⁵⁾

Suomi/Finland

Dr Markku TOIVONEN
Dr Eeva ALHAVA

Sverige

Prof. Bo ODLIND ⁽⁶⁾
Dr Per SJÖBERG

United Kingdom

Dr David JEFFERYS
Dr Patrick WALLER ⁽⁷⁾

⁽¹⁾ Ib Bo Lumholtz replaced Henning HOVGGAARD as of the 27 January 1998 meeting.

⁽²⁾ Manfred Haase replaced Reinhard KURTH as of the 27 January 1998 meeting.

⁽³⁾ Michalis Avgerinos replaced Marios MARSELOS as of the 27 January 1998 meeting.

⁽⁴⁾ Rogério Gaspar replaced José GUIMARAES MORAIS as of the 27 January 1998 meeting.

⁽⁵⁾ Cristina Sampaio replaced Miguel FORTE as of the 20 October 1998 meeting.

⁽⁶⁾ Bo Odland replaced Kjell STRANDBERG as of the 27 January 1998 meeting.

⁽⁷⁾ Patrick Waller replaced Susan WOOD (†) as of the 15 December 1998 meeting.

Annex 3

MEMBERSHIP OF THE COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

Chairman

Prof. Reinhard KROKER

Belgique/België

Prof. Paul-Pierre PASTORET
Mrs Françoise FALIZE

Danmark

Dr Helle HARTMANN FRIES ⁽¹⁾
Prof. Christian FRIIS

Deutschland

Dr Sabine EGLIT
Prof. Manfred MOOS

Ελλάδα/Greece

Prof. Christos HIMONAS ⁽²⁾
Mr Ioannis MALEMIS ⁽³⁾

España

Dr Luis Fernando CORBLAN
Dr Odon SOBRINO

France

Dr Jacques BOISSEAU
Mr Gérard MOULIN

Ireland

Dr Cyril O'SULLIVAN
(Vice-Chairman)
Mr Gabriel BEECHINOR

Italia

Prof. Agostino MACRI
Dr Gabriella CONTI

Luxembourg

Mr Marc WIRTOR
Dr Albert HUBERTY

Nederland

Dr Herman H. LENSING
Dr Johannes HOOGLAND ⁽⁴⁾

Österreich

Mag. Eugen OBERMAYR
Dr Johannes DICHTL

Portugal

Dr Margarida PRATAS
Prof. Carlos SINOGAS ⁽⁵⁾

Suomi/Finland

Dr Liisa KAARTINEN
Docent Satu PYÖRÄLÄ

Sverige

Dr Annika WENNBERG
Prof. Jan LUTHMAN

United Kingdom

Dr Michael RUTTER
Mr John O'BRIEN

⁽¹⁾ Helle Hartmann Fries replaced Anne PII as of the 13 January 1998 meeting.

⁽²⁾ Christos Himonas replaced Vassilios ELEZOLGLOU as of the 13 January 1998 meeting.

⁽³⁾ Ioannis Malemis replaced Dimistrios MIGOS as of the 13 January 1998 meeting.

⁽⁴⁾ Johannes Hoogland replaced Peter HEKMAN as of the 13 October 1998 meeting.

⁽⁵⁾ Carlos Sinogas replaced José BELO as of the 13 January 1998 meeting.

Annex 4

NATIONAL COMPETENT AUTHORITY PARTNERS

Addresses, contact points and further information on the national competent authorities may also be found on the new website launched by the national authorities in 1998
<http://heads.medagencies.org>

BELGIQUE/BELGIË

André PAUWELS
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ESPAÑA	Federico PLAZA PIÑOL Directore General de Farmacia y Productos Sanitarios Ministerio de Sanidad y Consumo Paseo del Prado 18-20 E-28014 Madrid Tel: (34-91) 227 67 00 Fax: (34-91) 596 15 47	Quintiliano PÉREZ BONILLA Director General de Producciones y Mercados Ganaderos Ministerio de Agricultura, Pesca y Alimentación José Abascal, 4 - 7ª planta E-28003 Madrid Tel: (34-91) 347 66 06 Fax: (34-91) 594 35 36
FRANCE	Jean-René BRUNETIÈRE Directeur-Général Agence du Médicament 143-147, blvd Anatole France F-93200 Saint-Denis CEDEX Tel: (33-1) 55 87 30 14 Fax: (33-1) 55 87 30 12	Jacques BOISSEAU Directeur Agence Nationale du Médicament Vétérinaire La Haute Marche Javené F-35133 Fougères Tel: (33-2) 99 94 78 72 Fax: (33-2) 99 94 78 99
IRELAND	Frank HALLINAN Chief Executive Officer Irish Medicines Board The Earlsfort Centre Earlsfort Terrace Dublin 2 Ireland Tel: (353-1) 676 49 71 Fax: (353-1) 676 78 36	Seamus HEALY Assistant Secretary Department of Agriculture/Food/ Forestry Agriculture House Kildare Street Dublin 2 Ireland Tel: (353-1) 607 24 34 Fax: (353-1) 676 29 89
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Annex 5

EMEA BUDGETS 1996 TO 1998

The summarised comparative budget statements for 1996 to 1998 are as follows:
(amounts expressed in ECUs)

	1996 ⁽¹⁾	1997 ⁽¹⁾	1998 ⁽²⁾
Revenues			
- fees	7 004 333	12 944 666	17 030 000
- EU subsidy	10 497 149	13 546 501	14 000 000
- other	372 209	552 087	870 000
Total revenue	17 873 692	27 043 254	31 900 000

Expenditure			
Title 1: Staff costs			
- salaries	5 029 510	9 051 341	12 743 000
- interim and other supporting persons	900 432	977 998	620 000
- other staff related expenditure	925 816	1 140 312	1 010 000
Title 2: Building and equipment			
- rent/charges	1 641 426	1 859 982	2 080 000
- expenditure on data processing	1 665 993	1 769 987	954 000
- other capital expenditure	117 599	439 811	165 000
- postage and telecommunications	326 177	463 346	410 000
- other administrative expenditure	805 561	968 037	922 000
Title 3: Operational expenditure			
- meetings	1 401 308	1 986 442	2 487 000
- evaluation of medicinal products	4 067 500	6 700 000	9 800 000
- translation	741 000	1 200 000	584 000
- studies and consultants	224 984	243 782	105 000
- publications	26 379	242 216	20 000
Total expenditure	17 873 692	27 043 254	31 900 000

Notes

⁽¹⁾ 1996 and 1997 budgets: outturn.

⁽²⁾ 1998 budget: final appropriations.

Annex 6

CPMP OPINIONS IN 1998 ON MEDICINAL PRODUCTS FOR HUMAN USE

Product Brand name INN Part A/B	Company Name Origin	Therapeutic area ATC Indication	Presentation Form Dose Number of presentations	EMA/CPMP Validation Opinion Active time Clock stop	Commission opinion received on Date of decision Date of notification OJ No.
Mirapexin pramipexole Part B	Pharmacia & Upjohn S	N04BC Idiopathic Parkinson disease	Tablets 0.125 mg, 0.25 mg, 1 mg, 1.25 mg, 1.5 mg 10 presentations	18.6.1996 18.6.1997 208 days 141 days	5.8.1997 23.2.1998 24.2.1998 OJ C 92, 23.3.1998, p. 2.
Viracept nelfinavir Part B	Agouron Pharmaceuticals US	J05 AX0 Antiviral agent	Tablet, Oral powder 250 mg, 50 mg/g 3 presentations	18.2.1998 24.9.1997 180 days 34 days	31.10.1997 22.1.1998 22.1.1998 OJ C 63, 27.2.1998, p. 4.
Quadramet Samarium [¹⁵³ Sm] Part B	Cis Bio International F	V10BX02 Therapeutic radiopharmaceutical for pain palliation	Solution for injection 1.5 ml, 2.3 ml, 3.1 ml 3 presentations	18.12.1996 22.10.1997 198 days 95 days	26.11.1997 5.2.1998 10.2.1998 OJ C 63, 27.2.1998, p. 4.
Primavax combined vaccines Part A	Pasteur Merieux MSD F	J07CA Bacterial and viral combined vaccines	Suspension for injection Diphtheria ≥ 30 IU Tetanus ≥ 40 IU r-HbsAG 5µg 1 presentation	21.1.1997 22.10.1997 201 days 68 days	21.11.1997 5.2.1998 10.2.1998 OJ C 63, 27.2.1998, p. 4.
Turvel trovafloxacin Part B	Roerig Farmaceutica I	J01M A Antibacterial agent	Tablets 100 mg, 200 mg 14 presentations	18.2.1997 22.10.1997 208 days 34 days	5.12.1997 8.7.1998 9.7.1998 OJ C 240, 31.7.1998, p. 2.
Turvel i.v. alatrofloxacin Part B	Roerig Farmaceutica I	J01M A Antibacterial agent	Concentrate for solution 100 mg, 200 mg, 300 mg 3 presentations	18.2.1997 22.10.1997 208 days 34 days	5.12.1997 3.7.1998 20.7.1998 OJ C 240, 31.7.1998, p. 2.
Trovan trovafloxacin Part B	Pfizer Ltd UK	J01M A Antibacterial agent	Tablets 100 mg, 200 mg 14 presentations	18.2.1997 22.10.1997 208 days 34 days	5.12.1997 3.7.1998 6.7.1998 OJ C 240, 31.7.1998, p. 2.
Trovan i.v. alatrofloxacin Part B	Pfizer Ltd UK	J01M A Antibacterial agent	Concentrate for solution 100 mg, 200 mg, 300 mg 3 presentations	18.2.1997 22.10.1997 208 days 34 days	5.12.1997 3.7.1998 6.7.1998 OJ C 240, 31.7.1998, p. 2.
Viramune nevirapine Part B	Boehringer Ingelheim D	J05AX04 Treatment of HIV-1 infected adults	Tablets 200 mg 2 presentations	20.6.1997 22.10.1997 125 days 0 days	21.11.1997 5.2.1998 10.2.1998 OJ C 63, 27.2.1998, p. 4.
Pylobactell ¹³ C-urea Part B	BSIA	V04CX Helicobacter pylori Test	Tablet 100 mg 1 presentation	18.12.1996 19.11.1997 163 days 158 days	13.2.1998 7.5.1998 8.5.1998 OJ C 164, 29.5.1998, p. 2.
Combivir lamivudine/ zidovudine Part B	Glaxo-Wellcome UK	J05AB20 HIV infected adults and children	Film-coated tablets 150 mg/300 mg 2 presentations	25.7.1997 19.11.1997 119 days 0 days	5.1.1998 18.3.1998 19.3.1998 OJ C 126, 24.4.1998.
Rebif Interferon beta-1a Part A	Serono CH	L03AA11 Multiple sclerosis	Solution for injection 6MIU 3 presentations	22.7.1996 17.12.1997 181 days 285 days	13.2.1998 4.5.1998 5.5.1998 OJ C 164, 29.5.1998, p. 2.

Product Brand name INN Part A/B	Company Name Origin	Therapeutic area ATC Indication	Presentation Form Dose Number of presentations	EMA/CPMP Validation Opinion Active time Clock stop	Commission opinion received on Date of decision Date of notification OJ No.
MabThera rituximab Part A	Hoffmann La Roche CH	L01 XX Stage III-IV follicular lymphoma	Concentration for solution for infusion 100 mg, 500 mg 2 presentations	21.3.1997 28.1.1998 179 days 132 days	9.3.1998 2.6.1998 3.6.1998 OJ C 200, 26.6.1998, p. 17.
Optison octafluoroprop- ane Part B	Mallinckrodt Medical D	V08D Ultrasound contrast Agent for use in echocardiography	Suspension for injection 0.22 mg/ml 2 presentations	21.3.1997 28.1.1998 192 days 122 days	4.3.1998 18.5.1998 19.5.1998 OJ C 200, 26.6.1998, p. 17.
Exelon rivastigmine Part B	Novartis Europharm CH	NO7 AA Alzheimer disease	Hard capsule 1.5 mg, 3 mg, 4.5 mg, 6 mg 16 presentations	18.4.1997 28.1.1998 186 days 97 days	3.3.1998 12.5.1998 12.5.1998 OJ C 164, 29.5.1998, p. 2.
Pylori-chek ¹³ C Urea Part B	Alimenterics BV NL	V04CX Helicobacter pylori Test	Powder for oral solution 100 mg 1 presentation	20.6.1997 25.2.1998 194 days 56 days	1.4.1998 15.6.1998 16.6.1998 OJ C 200, 26.6.1998, p. 17.
Echogen dodecafluoro- pentane Part B	Sonus Pharmaceuticals UK	V08DA Ultrasound contrast Agent for use in echocardiography	Aqueous emulsion for injection 20 mg/ml 1 presentations	18.12.1996 25.3.1998 176 days 270 days	5.5.1998 17.7.1998 20.7.1998 OJ C 269, 28.8.1998, p. 2.
Xenical orlistat Part B	Hoffmann La Roche CH	A08 A Antiobesity	Capsule 120 mg 6 presentations	2.1.1997 25.3.1998 183 days 255 days	5.5.1998 29.7.1998 30.7.1998 OJ C 269, 28.8.1998, p. 2.
Plavix clopidogrel Part B	Sanofi Pharma Bristol-Myers Squibb SNC F	BO1 AC04 Prevention of vascular ischaemia	Film-coated tablets 75 mg 3 presentations	16.5.1997 25.3.1998 200 days 112 days	28.4.1998 15.7.1998 16.7.1998 OJ C 240, 31.7.1998, p. 2.
Iscover clopidogrel Part B	Bristol-Myers Squibb Pharma EEIG F	BO1 AC04 Prevention of vascular ischaemia	Film-coated tablets 75 mg 3 presentations	16.5.1997 25.3.1998 200 days 112 days	28.4.1998 15.7.1998 16.7.1998 OJ C 240, 31.7.1998, p. 2.
Fortovase saquinavir Part B	Hoffmann La Roche CH	JO5 AX Combined treatment of advanced HIV	Capsule 200 mg 1 presentation	20.6.1997 22.4.1998 209 days 97 days	25.5.1998 20.8.1998
Evista raloxifene Part B	Eli Lilly Nederlands B.V. NL	ATC not yet available Prevention on post- menopausal osteoporosis	Film-coated tablets 60 mg 4 presentations	25.7.1997 22.4.1998 188 days 84 days	25.5.1998 5.8.1998 7.8.1998 OJ C 269, 28.8.1998, p. 2.
Celvista raloxifene Part B	Eli Lilly Nederlands B.V. NL	ATC not yet available Prevention on post- menopausal osteoporosis	Film-coated tablets 60 mg 4 presentations	25.7.1997 22.4.1998 188 days 84 days	25.5.1998 5.8.1998 6.8.1998 OJ C 269, 28.8.1998, p. 2.

Product Brand name INN Part A/B	Company Name Origin	Therapeutic area ATC Indication	Presentation Form Dose Number of presentations	EMA/CPMP Validation Opinion Active time Clock stop	Commission opinion received on Date of decision Date of notification OJ No.
NovoNorm repaglinide Part B	Novo Nordisk DK	A10BX02 Type 2 diabetes	Tablets 0.5 mg, 1 mg, 2 mg 7 presentations	25.7.1998 22.4.1998 199 days 97 days	5.6.1998 17.8.1998 18.8.1998 OJ C 297, 25.9.1998, p. 2.
HumaSPECT CR Kit votumumab Part A	Organon Teknika NL	V09IX Imaging of carcinoma of colon or rectum	Powder and solvent for solution for injection 10 mg 1 presentation	22.11.1996 27.5.1998 145 days 407 days	10.7.1998 25.9.1998 29.9.1998 OJ C 331, 29.10.1998, p. 1.
Comtess entacapone Part B	Orion FIN	N04BX02 Management of Parkinson disease	Film-coated tablet 200 mg 4 presentations	18.4.1997 27.5.1998 214 days 188 days	3.7.1998 16.9.1998 18.9.1998 OJ C 331, 29.10.1998, p. 1.
Comtan entacapone Part B	Novartis Europharm CH	N04BX02 Management of Parkinson disease	Film-coated tablet 200 mg 4 presentations	18.4.1997 27.5.1998 214 days 188 days	3.7.1998 22.9.1998 23.9.1998 OJ C 331, 29.10.1998, p. 1.
Aldara imiquinod Part B	Laboratories 3M Sante F	LO3A A External genital/ perianal warts	Cream 5%w/w 12.5 mg 1 presentation	20.6.1997 27.5.1998 209 days 132 days	30.6.1998 18.9.1998 22.9.1998 OJ C 331, 29.10.1998, p. 1.
Zartra imiquinod Part B	Laboratories 3M Sante F	LO3A A External genital/ perianal warts	Cream 5%w/w 12.5 mg 1 presentation	20.6.1997 27.5.1998 209 days 132 days	30.6.1998 18.9.1998 22.9.1998 OJ C 331, 29.10.1998, p. 1.
Viagra sildenafil Part B	Pfizer Limited UK	G04B E Erectile dysfunction	Film-coated tablet 25 mg, 50 mg, 100 mg 12 presentations	24.10.1997 27.5.1998 188 days 28 days	26.6.1998 14.9.1998 15.9.1998 OJ C 269, 28.8.1998, p. 2.
Patrex sildenafil Part B	Roerig Pharmaceutici Italiana S.p.A. I	G04B E Erectile dysfunction	Film-coated tablet 25 mg, 50 mg, 100 mg 12 presentations	24.10.1997 27.5.1998 188 days 28 days	26.6.1998 15.9.1998 16.9.1998 OJ C 269, 28.8.1998, p. 2.
Simulect basiliximab Part A	Novartis Europharm Ltd. UK	L04 AA02 Prophylaxis of acute rejection in renal transplantation	Powder and Solvent for solution for infusion 20 mg 1 presentation	24.10.1997 24.6.1998 153 days 91 days	3.8.1998 9.10.1998 14.10.1998 OJ C 331, 29.10.1998, p. 1.
Triacellucax bacterial vaccine Part A	Chiron S.p.A. I	JO7AJ Pediatric vaccine for diphtheria, tetanus and pertussis	Suspension for injection diphtheria ≥ 30 IU Tetanus ≥ 40 IU Pertactin 2.5µ 1 presentation	20.6.1997 23.7.1998 188 days 209 days	8.10.1998
Infergen interferon alphacon-1 Part A	Yamanouchi Europe B.V. JP	JO5AX Chronic hepatitis C	Solution for injection 9 µg 3 presentations	25.7.1997 23.7.1998 182 days 181 days	3.12.1998

Product Brand name INN Part A/B	Company Name Origin	Therapeutic area ATC Indication	Presentation Form Dose Number of presentations	EMA/CPMP Validation Opinion Active time Clock stop	Commission opinion received on Date of decision Date of notification OJ No.
Micardis telmisartan Part B	Boehringer Ingelheim International GmbH D	C09CA0 Hypertension	Tablets 40 mg, 80 mg 8 presentations	24.10.1997 23.7.1998 188 days 84 days	5.10.1998 16.12.1998
Pritor telmisartan Part B	Glaxo Group Ltd UK	C09CA0 Hypertension	Tablets 40 mg, 80 mg 10 presentations	24.10.1997 23.7.1998 188 days 84 days	20.9.1998 11.12.1998
Telmisartan Borhringer Ingelheim telmisartan Part B	Boehringer Ingelheim International GmbH D	C09CA0 Hypertension	Tablets 40 mg, 80 mg 8 presentations	24.10.1997 23.7.1998 188 days 84 days	5.10.1998 16.12.1998
Karvezide irbesartan/ hydrochlorotiazide Part B	Bristol-Myers Squibb Pharma EEIG F	C09DA Essential hypertension	Tablet 150/12.5 mg, 300/12.5 mg 6 presentations	19.12.1997 23.7.1998 153 days 63 days	21.8.1998 17.10.1998
CoAprovel irbesartan/ hydrochlorotiazide Part B	Sanofi Pharma Bristol-Myers Squibb SNC F	C09DA Essential hypertension	Tablet 150/12.5 mg, 300/12.5 mg 6 presentations	19.12.1997 23.7.1998 153 days 63 days	21.8.1998 15.10.1998
Forcaltonin recomb. salmon calcitonin Part A	Unigene UK	H05B A01 Hypercalcaemia of malignancy and Paget's Disease	Solution 50 IU/0.5 ml 2 presentations	26.9.1997 17.9.1998 210 days 147 days	20.10.1998
Prometax rivastigmine Part B	Novartis Europharm CH	NO7 AA Alzheimer disease	Hard capsule 1 mg, 1.5 mg, 3 mg, 4.5 mg, 6 mg 20 presentations	24.7.1998 17.9.1998 53 days	1.10.1998 4.12.1998
.... Part B	 D	NO7 Mild or moderate dementia of Alzheimer's type	Filmtablet 300 mg 5 presentations	19.11.1996 22.10.1998 182 days 519 days	
.... Part B	 D	NO7 Mild or moderate dementia of Alzheimer's type	Filmtablet 300 mg 5 presentations	19.11.1996 22.10.1998 182 days 519 days	
Rescupase saruplase Part A	Gruenenthal GmbH D	B01AD Thrombolytic therapy for acute myocardial infarction	Powder and solvent for solution for injection 20 mg 1 presentation	25.07.1997 22.10.1998 212 days 243 days	

Product Brand name INN Part A/B	Company Name Origin	Therapeutic area ATC Indication	Presentation Form Dose Number of presentations	EMA/CPMP Validation Opinion Active time Clock stop	Commission opinion received on Date of decision Date of notification OJ No.
Emadine emedastine Part B	Alcon Laboratories (UK) Ltd UK	S01GX Allergic conjunctivitis	Solution 0.05 % 2 presentations	19.12.1997 22.10.1998 182 days 127 days	2.12.1998
Temodal temozolomide Part B	SP Europe US	L01AX03 Recurrent malignant glioma	Capsules 5 mg, 20 mg, 100 mg, 250 mg 8 presentations	30.1.1998 22.10.1998 203 days 60 days	25.11.1998
Zaleplon Wyeth Medica Ireland zaleplon Part B	Wyeth US	N05CH01 Short term treatment of insomnia	Capsules 5 mg, 10 mg 6 presentations	30.1.1998 19.11.1998 182 days 113 days	
Sonata zaleplon Part B	Wyeth US	N05CH01 Short term treatment of insomnia	Capsules 5 mg, 10 mg 6 presentations	30.1.1998 19.11.1998 182 days 113 days	
Beromun tasonermin Part A	Boehringer Ingelheim International GmbH D	L03AA Adjunct to surgery for sarcoma of the limbs	Powder and solvent 0.2 mg/ml 1 presentation	24.10.1997 19.11.1998 188 days 204 days	
Zenapax daclicximab Part A	Roche Registration Ltd CH	L04A Prophylaxis of acute rejection in renal transplantation	Concentrate for solution for infusion 5mg/ml 2 presentations	26.9.1997 16.11.1998 205 days 214 days	
Cetrotide cetorelix Part B	Asta Medica D	G03X Prevention of premature ovulation in fertilisation treatment	Powder and solvent for for solution for injection 0.25 mg, 3 mg 4 presentation	27.2.1998 17.12.1998 173 days 121 days	
Refacto recombin.factor VIII Part A	Genetics Institute US	B02BD02 Control and prevention of haemorrhagic episodes	Powder and solvent for solution for injection 250 IU, 500 IU, 1000 IU 3 presentations	27.2.1998 17.12.1998 146 days 148 days	
Regranex becaplermin Part A	Janssen-Cilag International B.V. B	D03... Healing of full thickness Diabetic ulcers	Gel 100 µg/g 1 presentation	21.11.1997 17.12.1998 188 days 203 days	

Annex 7

CVMP OPINIONS ON MEDICINAL PRODUCTS FOR VETERINARY USE

Centralised applications

Product (a) Brand name (b) INN (c) Part A/B	Company (a) Name (b) Origin	Therapeutic area (a) Target species (b) Indication	Presentation (a) Form (b) Dosage (c) No of presentations	EMA/CVMP (a) Validation (b) Opinion (c) Active time (d) Clockstop	Commission (a) Opinion (b) Decision (c) Notification (d) Official Journal
(a) Nobivac-Porcoli (b) Inactivated vaccine (c) Part A	(a) Intervet International (b) NL	(a) Piglets (b) Neonatal colibacillosis	(a) Solution for injection (b) Multidose (c) 2	(a) 1.1.1995 (b) 27.7.1995 (c) 107 days (d) 94 days	(a) 24.8.1995 (b) 29.2.1996 (c) 4.3.1996 (d) OJ C 1996, 29.3.1996
(a) Pentofel (b) Vaccine (c) Part A	(a) Fort Dodge Laboratories (b) IRL	(a) Cats (b) Rhinotracheitis	(a) Solution for injection (b) Monodose (c) 3	(a) 16.6.1995 (b) 18.9.1996 (c) 208 days (d) 235 days	(a) 17.10.1996 (b) 5.2.1997 (c) 6.2.1997 (d) OJ C 63, 28.2.1997
(a) Quadrisol (b) Vedaprofen (c) Part B	(a) Intervet International (b) NL	(a) Horses (b) Control of inflammation	(a) Oral gel (b) 100mg/ml (c) 1	(a) 7.5.1996 (b) 16.7.1997 (c) 209 days (d) 235 days	(a) 14.8.1997 (b) 4.12.1997 (c) 5.12.1997 (d) OJ C 392, 24.12.1997
(a) Metacam (b) Meloxicam (c) Part B	(a) Boehringer Ingelheim (b) D	(a) Cattle (b) Adjunctive therapy in acute respiratory infection	(a) Solution for injection (b) 5mg/ml (c) 1	(a) 24.6.1996 (b) 16.7.1997 (c) 208 days (d) 180 days	(a) 14.8.1997 (b) 7.1.1998 (c) 8.1.1998 (d) OJ C 32, 30.1.1998
(a) Dicural (b) Difloxacin (c) Part B	(a) Fort Dodge Animal Health (b) NL	(a) Poultry (b) Antibacterial for systematic use	(a) Oral solution (b) 100mg/ml (c) 2	(a) 6.12.1995 (b) 11.6.1997 (c) 218 days (d) 337 days	(a) 11.7.1997 (b) 16.1.1998 (c) 20.1.1998 (d) OJ C 63, 27.2.1998
(a) Clomicalm (b) Clomipramine (c) Part B	(a) Ciba-Geigy (b) F	(a) Dogs (b) Treatment of anxieties	(a) Tablets (b) 5, 20 and 80mg (c) 3	(a) 13.11.1996 (b) 12.11.1997 (c) 210 days (d) 156 days	(a) 12.12.1997 (b) 1.4.1998 (c) 2.4.1998 (d) OJ C 126, 24.4.1998
(a) Neocolipor (b) Inactivated vaccine (c) Part A	(a) Rhône Mérieux (b) F	(a) Piglets (b) Passive immunisation against neonatal	(a) Suspension (b) 2ml (c) 5	(a) 2.10.1996 (b) 10.12.1997 (c) 191 days (d) 245 days	(a) 9.1.1998 (b) 14.4.1998 (c) 15.4.1998 (d) OJ C 126, 24.4.1998
(a) Nobilis IB4-91 (b) Live vaccine (c) Part B	(a) Intervet International (b) NL	(a) Poultry, chickens (b) Live vaccine against infectious	(a) Solution (b) 30ml/1000 doses (c) 5	(a) 16.10.1996 (b) 12.11.1997 (c) 210 days (d) 184 days	(a) 12.12.1997 (b) 9.6.1998 (c) corrigendum 5.8.1998 (d) OJ C 200, 26.6.1998
(a) Suvaxyn Aujeszky 783+O/W (b) Live vaccine (c) Part A	(a) Solvay Duphar (b) NL	(a) Pigs (b) Vaccine against Aujeszky disease	(a) Solution for injection (b) 2ml (c) 3	(a) 19.10.1996 (b) 8.4.1998 (c) 208 days (d) 328 days	(a) 8.5.1998 (b) 7.8.1998 (c) 10.8.1998 (d) OJ C 269, 28.8.1998

Establishment of maximum residue limits for new substances

Substance a) INN	Therapeutic area a) Target species	EMA/CVMP a) Validation b) Opinion c) Active time d) Clockstop	Commission a) Sent to Commission b) Date of regulation c) Official Journal
a) Difloxacin	a) Chicken, turkeys	a) 16.5.1995 b) 15.12.1995 c) 134 days d) 49 days	a) 13.2.1996 b) 8.7.1996 c) OJ L 170, 9.7.1996
a) Ketoprofen (extension)	a) Porcine	a) 15.5.1995 b) 22.3.1996 c) 85 days d) 217 days	a) 25.4.1996 b) 6.9.1996 c) OJ L 226, 7.9.1996
a) Diclazuril	a) Ovine	a) 12.12.1995 b) 24.4.1996 c) 104 days d) 0	a) 24.5.1996 b) 21.10.1996 c) OJ L 269, 22.10.1996
a) Eprinomectin	a) Bovine	a) 22.2.1996 b) 25.6.1996 c) 108 days d) 0	a) 26.7.1996 b) 8.1.1997 c) OJ L 5, 09.1.1997
a) Doramectin (modification)	a) Bovine	a) 14.5.1996 b) 24.7.1996 c) 70 days d) 0	a) 23.8.1996 b) 14.2.1997 c) OJ L 45, 15.2.1997
a) Praziquantel	a) Ovine	a) 3.8.1995 b) 18.9.1996 c) 187 days d) 152 days	a) 16.10.1996 b) 25.4.1997 c) OJ L 110, 26.4.1997
a) Moxidectin (modification)	a) Bovine, ovine	a) 12.6.1996 b) 18.9.1996 c) 97 days d) 0	a) 16.10.1996 b) 25.4.1997 c) OJ L 110, 26.4.1997
a) Difloxacin (modification)	a) Chicken, turkeys	a) 10.7.1996 b) 23.10.1996 c) 104 days d) 0	a) 19.11.1996 b) 25.4.1997 c) OJ L 110, 26.4.1997
a) Ivermectin (extension)	a) Deer	a) 20.8.1996 b) 11.12.1996 c) 86 days d) 0	a) 9.1.1997 b) 23.4.1997 c) OJ L 106, 24.4.1997
a) Amitraz (extension)	a) Bees	a) 18.10.1996 b) 12.2.1997 c) 115 days d) 0	a) 12.3.1997 b) 24.9.1997 c) OJ L 263, 25.9.1997
a) Doramectin (extension)	a) Swine, ovine	a) 10.6.1996 b) 12.2.1997 c) 118 days d) 127 days	a) 12.3.1997 b) 24.9.1997 c) OJ L 263, 25.9.1997
a) Cefazolin (extension)	a) Ovine, caprine	a) 5.6.1997 b) 10.9.1997 c) 97 days d) 0	a) 10.10.1997 b) 16.1.1998 c) OJ L 11, 17.1.1998
a) Isoflurane	b) Equine	a) 13.5.1996 b) 7.5.1997 c) 200 days d) 158 days	a) 5.6.1997 b) 23.2.1998 c) OJ L 53, 24.2.1998
a) Teflubenzuron	a) Fish	a) 20.1.1997 b) 7.5.1997 c) 105 days d) 0	a) 5.6.1997 b) 23.2.1998 c) OJ L 53, 24.2.1998

Substance a) INN	Therapeutic area a) Target species	EMEA/CVMP a) Validation b) Opinion c) Active time d) Clockstop	Commission a) Sent to Commission b) Date of regulation c) Official Journal
a) Florfenicol (extension)	a) Fish	a) 29.1.1996 b) 16.7.1997 c) 129 days d) 404 days	a) 12.8.1997 b) 18.3.1998 c) OJ L 82, 19.3.1998
a) Moxidectin (extension)	a) Equidae	a) 9.4.1997 b) 16.7.1997 c) 96 days d) 0	a) 12.8.1997 b) 18.3.1998 c) OJ L 82, 19.3.1998
a) Praziquantel (extension)	a) Equidae	a) 15.9.1997 b) 14.1.1998 c) 120 days d) 0	a) 9.2.1998 b) 27.5.1998 c) OJ L 154, 28.5.1998
a) Meloxicam	a) Bovine	a) 28.3.1996 b) 11.6.1997 c) 212 days d) 229 days	a) 9.7.1997 b) 17.7.1998 c) OJ L 205, 22.7.1998
a) Tilmicosin (extension)	a) Chickens	a) 14.7.1997 b) 12.11.1997 c) 111 days d) 0	a) 12.12.1997 b) 9.9.1998 c) OJ L 250, 10.9.1998
a) Valnemulin	a) Porcine	a) 2.8.1996 b) 6.5.1998 c) 207 days d) 641 days	a) 5.6.1998 b) 27.11.1998 c) OJ L 320, 18.11.1998
a) Alfaprostol (extension)	a) Rabbits	a) 15.5.1997 b) 6.5.1998 c) 200 days d) 362 days	a) 5.6.1998 b) 27.11.1998 c) OJ L 320, 28.11.1998
a) Rifaximin	a) All mammalian food producing species	a) 9.1.1997 b) 6.5.1998 c) 180 days d) 508 days	a) 5.6.1998 b) 27.11.1998 c) OJ L 320, 28.11.1998
a) Bronopol	a) Salmonidae	a) 7.5.1997 b) 10.6.1998 c) 198 days d) 202 days	a) 10.7.1998 b) 11.12.1998 c) OJ L 337, 12.12.1998
a) Flumethrin	a) Bovine, ovine, caprine, honey bees	a) 11.11.1996 b) 10.6.1998 c) 197 days d) 380 days	a) 10.7.1998 b) 11.12.1998 c) OJ L 337, 12.12.1998
a) Enrofloxacin (modification)	a) Bovine, porcine, poultry	a) 3.2.1997 b) 8.7.1998 c) 183 days d) 336 days	a) 30.7.1998 b) 17.12.1998 c) OJ L 343, 18.12.1998
a) Enrofloxacin (extension)	a) Dairy cattle, ovine, rabbits	a) 3.2.1997 b) 8.7.1998 c) 183 days d) 336 days	a) 30.7.1998 b) 17.12.1998 c) OJ L 343, 18.12.1998
a) Sodium 2-methyl- 2-phenoxy- propionate	a) Bovine, porcine, caprine, equidae	a) 26.11.1996 b) 8.7.1998 c) 201 days d) 388 days	a) 30.7.1998 b) 17.12.1998 c) OJ L 343, 18.12.1998
a) Ivermectin	a) Deer	a) 20.8.1996 b) 8.7.1996 c) 170 days d) 518 days	a) 30.7.1998 b) 17.12.1998 c) OJ L 343, 18.12.1998
a) Diethylene glycol monoethyl ether	a) Bovine, porcine	a) 14.2.1997 b) 8.7.1998 c) 170 days d) 337 days	a) 30.7.1998 b) 17.12.1998 c) OJ L 343, 18.12.1998

Annex 8

REFERENCE DOCUMENTS

(a) EU official publications

- Council Regulation (EEC) No 2309/93 as amended (OJ L 214, 24.8.1993, p.1)
- Council Regulation (EEC) No 2377/90 as amended (OJ L 224, 18.8.1990, p.1)
- Council Directive 75/319/EEC as amended (OJ L 147, 9.6.1975, p.13)
- Council Directive 81/851/EEC as amended (OJ L 317, 6.11.1981, p.1)
- Council Regulation (EC) No 2743/98 (OJ L 345, 19.12.1998, p.3)
- EMEA budget statement for the financial year 1998 (OJ L 57, 26.2.1998, p.1)

The texts of these and other provisions may be also be found in the series 'Rules governing medicinal products in the European Community'. These publications, along with copies of the Official Journal, are available from:

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The texts are also available on the EudraLex Internet site at <http://dg3.eudra.org/eudralex/index.htm>

(b) EMEA documents

- First General Report on the Activities of the European Agency for the Evaluation of Medicinal Products 1995 (ISBN 92-827-7491-0, Office for Official Publications of the EU)
- Second General Report on the Activities of the European Agency for the Evaluation of Medicinal Products 1996 (ISBN 92-9155-002-7, Office for Official Publications of the EU)
- Third General Report on the Activities of the European Agency for the Evaluation of Medicinal Products 1997 (ISBN 92-9155-010-8, Office for Official Publications of the EU)
- Statement of principles governing the partnership between the national competent authorities and the EMEA (EMEA/MB/013/97)
- Financial Regulation applicable to the budget of the EMEA (EMEA/MB/011/97)
- Decision of the Executive Director of 3 December 1997 on rules on access to documents of the EMEA

These and other documents are available either on the Internet at <http://www.eudra.org/emea.html> or by writing to:

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